

Validation documentation  
*APIs & excipients, solid*

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January 19, 2018



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## Introduction

The unequivocal proof of the identity of pharmaceutical raw materials based on a monograph or traditional alternative methods is work-intensive, time-intensive and economically often no longer makes sense. Near-infrared spectroscopy (NIR) provides a new means here. It enables relatively easy, fast and nonetheless safe identity testing via the preparation and evaluation of spectra.

The analysis system *Apo-Ident* was developed specially for pharmacy use. Pharmacists have the duty to check the identity of all raw materials for extemporaneous products in their pharmacies. This normally takes place based on the monographs for the respective substances in the European Pharmacopoeia. But also NIR spectroscopy is described in the European Pharmacopoeia as an identification method which, as opposed to the methods incorporated in the respective monographs, is approved for testing [1] (quotation translated)

*with the prerequisite that the same results (“namely the determination of the identity” [2]), (quotation translated) are achieved as with the described methods and instruments.*

The *Apo-Ident* analysis system serves to identify raw materials for prescriptions in the defined manner according to *ApBetrO* [Pharmacies Rules and Regulations] §§ 6 and 11 at pharmacies (NIR spectroscopy as an alternative testing method). *Apo-Ident* consists of three components:

- An *NIR spectrometer*, which records the spectra of non-preprocessed raw materials in a measuring glass in diffuse reflection or transfection.
- The *QuickStep* spectroscopy software controls the instrument and records the spectra and user inputs via a pharmacy-specific software plug-in. It also generates the test protocol for documentation of the testing and storage of the printout to be signed in the pharmacy.
- The software module *IdentModule* incorporates *reference databases*. The spectra from the *QuickStep* software are presented to it for evaluation.

NIR spectroscopy is a very powerful analytical method. It is also able to establish the identity of several chemical compounds and mixes in as far as an appropriate database (technically correct: a [chemometric model](#)) was created. Identity testing with *Apo-Ident* is a very safe, very fast and easy to operate analytical method for testing a large number of raw materials.

## Context of this document

The suitability of the instrument, method and database is proven as follows:

- *NIR spectroscopy as a method for identity testing*: The *Ph. Eur.* [3] describes NIR spectroscopy in *Section 2.2.40* as an analytical method which is also suitable for the identification of raw materials. Therefore, validation of the method as such is not necessary.
- *Performance of the instrument*: The *Ph. Eur.* [3] furthermore describes the apparatus and the testing of its performance in *Section 2.2.40*. The document *Erfüllung von 2.2.40 Ph. Eur. durch Apo-Ident* [4] compares the implementation by *Apo-Ident* with this monograph in order to prove that *Apo-Ident* meets the specifications of the Pharmacopoeia. Each individual instrument delivered to a pharmacy is qualified in accordance with the tests described in “*Control of Instrument Performance*”. In this test, the unit consisting of analysis instrument hardware and the *QuickStep* spectroscopy software is assessed. The result is documented in a test protocol which is kept at the pharmacy.
- *Validation of the database* is documented separately for each substance class. The report at hand documents the substance class *APIs & excipients, solid*.

The *Arbeitsgemeinschaft der Pharmazieräte Deutschlands (APD)* [Working Group of German Pharmacy Inspectors] has clarified the following in its resolution dated October 16, 2013 ([5], quotation translated):

*NIR is a testing method incorporated in the Pharmacopoeia. The testing quality depends on the quality of the database stored. The APD views the use of NIR instruments in case of ensured validation of the databases used in conjunction with it as one of several options for identity testing.*

The APD defined more precisely ([6], quotation translated) on October 1, 2014:

*The use of near-infrared is a recognised testing method according to Ph. Eur. 8. For the use of NIR instruments in pharmacies for testing the identity of raw materials, sufficient and verifiable validation of the instrument used is required. The quality of the database stored by the instrument manufacturer is decisive for quality. Batch-specific differences with the same original substances must be taken into account if present.*

So NIR is basically suitable. The validity of the reference database is proven with the existing validation documentation.

## Validity scope of this document

This validation documentation describes the results of the validation of the reference database for the substance class *APIs & excipients, solid*. Validation documentation is created for each published version of the reference database for all substance classes incorporated.

The reference database is incorporated in the software module *IdentModule*. During identification testing with *Apo-Ident*, spectra which are used for evaluation purposes are presented to it by the *QuickStep* software. In the same manner, the *IdentModule* is presented all validation spectra successively during the validation runs for evaluation purposes. The *IdentModule* responds respectively (without taking the initial assumption into account) with the identified substance or rejects it as unknown. The correctness of this response is checked for each possible initial assumption and counted.

The results are summarised for each substance and reproduced in this document.

- The database is exclusively established from spectra which have been recorded by *HiperScan GmbH* for traceable samples in pharmaceutical quality.
  - The samples are procured via typical pharmacy sources (*DAC III.2.: Bezugsquellennachweis für Rezepturbestandteile [reference source for prescription components]* [7]).
  - A valid manufacturer's certificate exists (content, purity and identity of the batch).
  - The identity was confirmed by a certified test laboratory or *HiperScan GmbH*.
- Each version of the reference database (every update) is validated in-full.
  - In three separately evaluated validation runs, calibration spectra, spectra from independent samples and spectra from independent field samples (described further below as *Type A*, *B* or *C*) are presented to the *IdentModule* for evaluation.
  - Here, no single *false positive* result may arise.
  - Here, the various substance classes are also tested for reciprocal rejection, where this is objectively justified (see *Summary section*).
- For each individual substance, the unambiguous identifiability with *Apo-Ident* and the demarkation against all other database substances is proven.

## Validation concept

*Chemometrics* is a statistical technique for the extraction of relevant chemical information from spectra. In mathematics, this method is described as *multivariate data analysis*. Chemometrics proceeds here as follows:

1. Collection of spectra for the *calibration sample*. The results (identities) of the calibration sample must be known. The calibration samples must be representative for the samples which are to be evaluated later. Therefore, they must take the various possible (physical) compositions into account. (Therefore, sourcing calibration samples for NIR from the specialist trade is superior to the use of CRS reference substances.)

2. The first mathematical step is *calibration*. Here, the [chemometric model](#) is calculated from the *calibration sample spectra* ([reference spectra](#)) and limits as well as some parameters are stipulated. The chemometric model is used later to calculate the analysis result (*prediction*).
3. Collection of further spectra for the *validation sample* which should be independent of the *calibration sample*. The results (identities) of the *validation sample* must also be known. The textbook suggests a random sample with a normal scope of 25 % to 50 % of the *calibration sample* [8].
4. The second technical data step is *validation*. Here, the [chemometric model](#) created is evaluated based on the spectra of the *validation samples*. As validation parameters for the identification, the *Ph. Eur. Section 2.2.40* [3] specifies the [specificity](#) and [robustness](#).

The validation step according to the textbook has the target of estimating the performance capability of the model created based on a random sample. In order to achieve the best possible precision, attention is paid to the calibration sample. In the field of pharmaceuticals, the safety of the method has priority. In order to be able to [validate](#) the model within the regulatory scope, the validation step must include probative force. For this purpose, the validation sample must be *representative and complete* in order to enable the testing of all cases.

A *sufficient number of batches* must be secured for validation because validation finally proves whether the number of batches in calibration suffices.

Each substance is validated individually. The validation results are documented per substance in this document. Moreover, the documents show how many and which batches have been used for creating the model or model validation.

At least one certificate is taken in for each substance from an accredited test laboratory for the independent testing of identity of the sample. The identification number of the corresponding test certificate is listed in the report, enabling traceability of a substance tested according to the monographs in the Pharmacopoeia.

## Model creation procedure and validation runs

The safety of the [chemometric models](#) is guaranteed by several measures during model creation, of which the validation step is the final one. Normally, the procedure is as follows. It is in particular valid for the active pharmaceutical ingredients (APIs) *solid API excipients, liquid/semi-solid API excipients (with a test certificate), narcotics - solid medicinal substances and drugs*. If, for individual substance classes, variations are required, they are depicted in the section [Particularities of individual substance classes](#).

### 1. Collecting the reference spectra (calibration sample)

- a) Procurement of the samples from the same sources from which pharmacies source their raw material for compounding (Caelo, Fagron, Euro-OTC, ..., see also *DAC III.2. Bezugsquellen-nachweis für Rezepturbestandteile* [Sources of supply for compounding] [7]).
- b) Testing the suitability according to *ApBetrO* [Pharmacies Rules and Regulations] §§ 6, 11, that is to say the availability of a valid manufacturer certificates via identity, purity and contents of the batch.
- c) Recording standard 40 spectra of the sample in different positions, as a standard on four instruments. Here, handling and presentation of the samples as later in the pharmacy.
- d) Visual checking for anomalies in the spectra. In case of indications of measurement errors, measurement must be repeated. If a signature is missing in the spectrum, the substance may be excluded from the start as not promising (the spectra are nonetheless entered in the database validation as independent *Type B* spectra).
- e) Testing identity. For each substance, a certificate of correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the respective following substance page of this validation documentation the [Mahalanobis distance](#) to this reference sample is specified as well

as the *Mahalanobis distance* to the next non-identical substance. Such samples underline the statistical spread of the original reference substance, but cannot add any new characteristics of the substance.

*HiperScan GmbH* cooperates with some suppliers as follows: the raw materials supplier takes a sufficiently large sample in his incoming goods area so that part of it can be used for recording the NIR spectra. The remainder of the sample goes to analytics for market approval. The manufacturer's batch certificate emerges from these identity, contents and purity tests, which consequently also prove the correct identity of the NIR reference sample. Therefore, the NIR spectra are suitable for structuring the database (*Type A*) and can also optionally be used for validation (*Type B*). The samples which this applies to are marked in the validation report with a footnote.

- f) If the identity of the new sample is proven, it is declared as a reference sample and the spectra are approved for structuring the database.

## 2. Generating the chemometric models (calibration)

- a) Determination of the transformation matrix from the reference spectra using variance maximisation [8, 9]. (All reference spectra are always included, even if only a few spectra are added for an update.) All reference spectra receive the same data pre-treatment, which is also later applied to all measurement spectra in the field (in the pharmacies).
- b) Checking that the number of principal components used is still sufficient.
- c) Calculating the limits for each substance from the spread of the reference spectra. The calculation regulation is identical for each substance in a substance class.
- d) Checking the distances between the limits of the separable substances: the distance matrix incorporates the *Mahalanobis distances* from each substance to all the others. If a distance is less than 10, both two substances must be declared as inseparable or *both two* must be removed from the database. (The spectra of removed substances remain as independent *Type B* spectra in the validation.)
- e) Testing the model based on the reference spectra. If *false positive* results arise, you must proceed as in the case of *Mahalanobis distances* which are too small.
- f) If chemometric models are available for all substance classes which meet both criteria (distance matrix and no *false positives*), they are joined together with the evaluation algorithms as an *IdentModule* and encrypted. This unit can no longer be changed. Its overall function is tested by validation.

## 3. Set of validation spectra (validation samples)

The following is provided for validation:

- a) *Type A*: The reference spectra = calibration spectra from which the database was established. These also include spectra from substances which the *chemometric model* should not identify, but were also recorded during generation in order to increase selectivity. (As a result, the model "learns" to differentiate from other substances which are actually unknown to it.)
- b) *Type B*: Spectra from independent samples not included in the generation of the respective model received but were measured by *HiperScan GmbH*. These also include reference spectra from other substance classes and spectra which are not declared as reference spectra.
- c) *Type C*: Spectra from independent field samples. These measurements were recorded under normal everyday conditions by pharmacy staff. The spectra belong both to substances of the substance class to be examined and to substances from different classes.

All manufacturers' batches from which spectra flow into the validation are listed by substance in this document: for substances included in the substance class *APIs & excipients, solid* in the respective validation reports; otherwise in attachments *A*, *B* and *C*.

Furthermore remains valid: validation spectra may only be removed if a spectrum error can be proven. Here, the spectra are not deleted, but instead placed on a *blacklist* incorporating the reason, date and initials in the commentary.

The section *Particularities of individual substance classes* treats the other substance classes from which *Type B* and *Type C* spectra are cited for validation purposes.

#### 4. Validation runs and approval

- a) Validation spectra are transferred holistically to the *IdentModule* for evaluation in the same way as the spectroscopy software *QuickStep* transfers measured spectra.
- b) Following the provision of each spectrum, the *IdentModule* responds as to whether it has recognised a substance and which substance was recognised.
- c) The correctness of this response is checked for each possible initial assumption (each measurable substance with the substance class) and counted according to *true negative*, *false negative*, *true positive* and *false positive*. These figures are provided for each substance and additionally in the section *Summary*, separated according to types *A*, *B* and *C*.
- d) No *false positive* results whatsoever are permissible.
- e) If the criterion is also met for all substance classes, the *IdentModule* is approved.

#### Particularities of individual substance classes

Basically, *HiperScan GmbH* procures and tests the manufacturer's certificate for the batch, commissions external testing of the identity of the sample or carries it out independently and stores the certificates. As described, this process is established for the Pharmacopoeia substances, that is to say for substance classes **APIs & excipients, solid**, **APIs & excipients, liquid/semi-solid (with analysis certificate)**, **Narcotic substances, liquid/semi-solid** and **Drugs**. Therefore, *HiperScan GmbH* is able to furnish proof of the identity of the reference samples. In case of manufacturer-specific substance classes and others, individual steps are organised differently in-part:

The substance class **APIs & excipients, liquid/semi-solid (other)** (often described as cosmetics) incorporates substances for which no specification of the requirements of the pharmaceutical quality is determined, neither in a Pharmacopoeia monograph, a DAC/NRF monograph nor via a manufacturer's specification. Consequently, neither the identity nor contents can be tested independently. No certificates whatsoever exist for the reference samples. So here, merely the matching of the sample with former samples of this product is established and confusion with the other substances is ruled-out. (If the manufacturer of such a substance prepares a specification, determines testing methods and provides manufacturer's certificates in accordance with *ApBetro* [Pharmacies Rules and Regulations] §§ 6, 11, *HiperScan GmbH* can assign the substance to the substance class *APIs & excipients, liquid/semi-solid (with analysis certificate)* again in the future).

Substance class **HCK – nutritional supplements (Hepart)** contains the HCK micro-nutrients from the Swiss company *Hepart AG*. *HiperScan GmbH* receives the reference samples directly from the manufacturer. For each reference sample, *HiperScan GmbH* also receives manufacturer's certificates and keeps these. New checking of the identity of the reference sample is not carried out by *HiperScan GmbH*. The identity of the reference samples is therefore documented by *Hepart AG*. The spectra of all batches provided by *Hepart AG* are recorded by *HiperScan GmbH* and entered in the database.

Also, for the substance class **PhytoComm** (TCM-Granulated herbal extracts of the manufacturer *PhytoComm*) spectra for all useable batches are recorded by *HiperScan GmbH* and entered in the database. The supplier organises the respective tests themselves and keeps the test certificates.

A new evaluation option was created for the class *PhytoComm* with the update 2016-01. As the risks are considerably fewer than those from chemical agents, the pharmacist can specify a reasonable criterion for the *specificity* in accordance with internal risk estimation. The database for this is created without taking safety distances into account and no criterion is determined in advance for the *specificity*. Instead, the *specificity* for testing the identity with this concrete substance is calculated in the validation for each substance and provided with the measurement result. The pharmacist then judges himself whether this safety is reasonable with regard to the risk of the substance.



Additionally, a statistical forecast is provided for the *specificity* which is determined according to the *Rule of Three* [10, 11]. For this forecast, it is assumed that there would have been three wrong results more and is provided with a lower limit for *specificity*. This value has a special meaning if a *specificity* of 100 % is achieved for a substance during validation. In this case, the lower limit allows conclusions regarding the scale of existing safety for which with an endless number of validation spectra a value of less than 100 % is to be assumed.

If, for example 14000 spectra not belonging to the substance are presented and no *false positive* classification is made, a hypothetical number of three *false positive* results is assumed (*Rule of Three* [10, 11]) and the *specificity* is defined with 100.0000 % (> 99.9786 %). Here, it applies that the higher the number of validation spectra which form the statistical basis, the better the *specificity* calculated via the lower *specificity* limit will be approximated.

The positive result of the identity test using *Apo-Ident* establishes that the sample spectrum is in accordance with a batch of the specified granulate from the supplier *PhytoComm*, whereby all useable batches from the supplier are known.

## Significance of testing with *Apo-Ident*

The analysis result is determined using sophisticated statistical methods according to state-of-the-art science and technology. Chemical and pharmaceutical knowledge is applied for the selection of the samples from which the calibration spectra and validation spectra are recorded. Otherwise it does not influence the further steps of model creation.

Verbally, the statement of the analysis result can be expressed as follows. Here “*the spectra match*” means that the criteria *Mahalanobis distance*, *outlier analysis* and *correlation* are met as shown in *Erfüllung von 2.2.40 Ph. Eur. durch Apo-Ident* [4]. “The spectra do not match”, on the other hand, means that at least the criterion *Mahalanobis distance* is not met.

The positive analysis result “*was identified as ...*” is very meaningful because both the quantity of substances to be taken into account and the number of underlying samples is very comprehensive.

1. The spectrum of the sample measured matches spectra of the defined substance.
2. The spectrum of the sample measured does not match any spectrum of any other substance in this substance class. Therefore, all other substances can be clearly ruled-out.
3. As the spectra from other substance classes were used for validation, it is proven that no spectrum of one of these other substances matches the defined substance. (All substance classes with which a spectrum comparison is possible and makes sense are used for validation. This is documented for each substance class in the section *Summary*.)
4. If the defined substance belongs to a *substance group* which in itself is not clearly separable with *Apo-Ident*, matching with the spectra of one or several substances in this group is confirmed. Which of these substances it actually is cannot be determined clearly. All other substances are excluded analogous to 2 and 3.

On the other hand, a negative analysis result “*was not identified as ...*” means:

1. The substance offered could not be recognised based on the spectrum of this sample.
2. The identity of this sample is not confirmed.
3. Testing must be repeated in accordance with the specifications of the Pharmacopoeia.

## Conclusion

NIR spectroscopy is a testing method incorporated in the Pharmacopoeia. In case of successful database validation, it is a possible method for identity testing [5]. *Apo-Ident* meets the criteria of the *European Pharmacopoeia* as a near-infrared spectrometer and proves the validity of the reference database with the existing validation documentation. This means that *Apo-Ident* can be used as an alternative testing method for testing raw materials at pharmacies.



## Explanation of terminology

The following section serves to explain or define specialist terminology which is required in order to understand this document. If necessary, definitions for the analysis system *Apo-Ident* are defined more precisely.

**The term database** is used in this document exactly as in the *Ph. Eur. Section 2.2.40* [3] synonymous with [chemometric model](#). In order to differentiate the databases which are relatively independent of each other, *HiperScan GmbH* frequently also uses the term [substance class](#) (primarily in the plural). On the other hand, the spectra used to structure the database are termed spectrum collection and not database.

**Substance classes** are units of the organisational structure of the *IdentModule*. The substance classes are substance [databases](#) which are also broadly independently subscribable. On the one hand, the liquid and semi-solid substances are separated from the solid powders because they are measured against different references and therefore the spectra cannot be compared. On the other hand, for example the Pharmacopoeia substances are kept separated from the manufacturer-specific database *PhytoComm* for TCM (traditional Chinese medicine) raw materials.

The individual substance classes need only be limited against each other in-part. Often, no risk of confusion exists because they can only be procured from different sources. On the other hand, in several cases we handle substances which need not be distinguished. For example, *Huang Qi* granulate from the company *PhytoComm* neither needs to be delimited from *Huang Qi* granulate from the company *HerbaSinica* nor is matching required. Respectively one single [chemometric model](#) is behind a substance class. (Even if several reciprocally secured chemometric models would be permissible.) The terms *substance class*, *chemometric model* and *databases* are mostly used here as synonyms.

**A substance group** respectively summarises all the substances within a [substance class](#) which cannot safely be distinguished from one another based on their NIR spectra. However, all the other substances in the database can be excluded.

**The formation of subgroups** is mentioned in the *Ph. Eur. Section 2.2.40* [3]. In this manner, technical restrictions in case of extensive databases can be avoided and it is possible to prepare individual subgroups with different spectrum pre-treatment. Validation of the subgroups against each other is required. *HiperScan GmbH* has solved these technical restrictions and doesn't use any subgroups within a substance class any longer.

**Principal component analysis (PCA)** [8, 9] is a multivariate statistics process or multivariate data analysis. It serves to structure, simplify and illustrate comprehensive data records by describing a large number of statistical variables by describing a lower number of linear combinations (the *principal components*) which are as significant as possible. In the *Apo-Ident IdentModule*, *PCA* is used to evaluate the recorded spectrum data (corresponding with *Ph. Eur. 2.2.40* [3]).

**The term validation** is defined in both relevant contexts here with different (even if related) meanings.

Within the sense of the expert discipline of *chemometrics*, validation is a process step when creating a [chemometric model](#): after a transformation matrix, limits and various parameters have been calculated or determined from a set of reference spectra during the course of the calibration step [8, 9], the validation step determines the performance capability of the model (selectivity, precision, ...) based on the validation spectra. Normally, random sampling is planned here. In order for the validation to gain strength of proof, the validation spectrum set must be selected with an appropriately wide scope (*representative* and *complete*). The terms *validation run* and *validation step* always actually mean the process step in this sense.

In the regulatory sense (of pharmaceutical production), validation is the documented proof that a process or system meets the previously specified requirements reproducibly when applied practi-

cally. In this sense, the *Apo-Ident* databases only become validated databases with the validation documentation, which this document is part of.

The *European Pharmacopeia* uses the term validation in *Section 2.2.40* within the sense of the specialist discipline of *chemometrics* [3].

**The robustness** of a process is the property of only being influenced by environmental fluctuations (e.g. temperature or humidity) a little. A method is robust if the environmental conditions do not or hardly falsify the final result.

**The specificity** of a classification (of a [chemometric model](#)) is the [true negative rate](#).

**The recognition rate** (also sensitivity) is the [true positive rate](#). It defines in how many percent of cases a correctly set up substance is actually confirmed.

**The true negative rate** describes the share of spectra correctly classified as non-identity during validation. This is equivalent to correct classification. It means that a substance *A* within identity checking as substance *B* is judged as “*not identified*”. The *true negative rate* is equivalent to the conditional frequency

$$h(\text{rejected}|\text{genuinely no identity}) = \frac{r_n}{r_n + f_p}$$

with  $r_n$  as the total number of *true negative* classifications and  $f_p$  as the total number of *false positive* classifications. For successful validation of an *IdentModule*, all spectra presented belonging to this category must be classified as *not in accordance*.

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of this number. The weight of each spectrum of a substance/substance group *i* therefore results as

$$w_i = \frac{1}{n_i}$$

with  $n_i$  number of spectra in this substance/substance group. This weighting ensures that the overall result cannot be enhanced by adding especially large numbers of spectra from easily separable substances.

**The true positive rate** describes the share of spectra correctly classified as identity during validation. This is equivalent to correct classification. It means that a substance *A* within identity checking as substance *A* is judged as “*identified*”. The *true positive rate* is equivalent to the conditional frequency

$$h(\text{identified}|\text{genuine identity}) = \frac{r_p}{r_p + f_n}$$

with  $r_p$  as the total number of *true positive* classifications and  $f_n$  as the total number of *false negative* classifications. The *true positive rate* is a measure for the recognition rate of the validated *Apo-Ident IdentModule*.

In order to ensure that each substance is received with the same weight, the spectra are weighted as described for the [true negative rate](#).

**The true negative result** describes a spectrum correctly classified as non-identity during validation. It is equivalent to correct classification. It means that a substance *A* within identity checking as substance *B* is judged as “*not identified*”.

**The false positive result** describes a spectrum falsely classified as non-identity during validation. This is the most critical type of possible false classification. It means that a substance *A* within identity checking as substance *B* is judged as “*identified*”. For successful validation of an *IdentModule*, a number of false positive events of zero are demanded for all spectra entering the validation. The exception to this restriction is the class of TCM granulates from the company *PhytoComm* as described under [Particularities of individual substance classes](#).

**The true positive result** describes a spectrum correctly classified as identity during validation. It is equivalent to correct classification. It means that a substance *A* within identity checking as substance *A* is judged as “*identified*”.

**The false negative result** describes a spectrum falsely classified as non-identity during validation. It is equivalent to false classification. It means that a substance *A* within identity checking as substance *A* is judged as “*not identified*”.

**The ‘Rule of Three’** says that with a probability of 95 % the next random sample of the same size no more than three false results are to be expected if no false result existed in the existing random sample [10, 11].

The *specificity* and *recognition rate* are determined both globally and from the validation runs for all substances. The information is supplemented with the hypothetical value if there had been three false results more. The percent information is provided in parentheses with the “greater than” symbol ‘>’, e.g. *specificity* 100.000 % (>99.983 %) if 17 567 false spectra have been presented without one single *false positive* result. The larger the statistical basis, the lower the influence of the hypothetical false results.

**The Mahalanobis distance** is a distance measure between two points in *n*-dimensional vector space. Here, the respective direction component of the distance to *standard deviation* [12] of an *n*-dimensional distribution is standardised. In case of the *principal component analysis* [8, 9] this standardisation relates to the distribution of the respective calibration data set for a classification (substance/substance group) in the *principal component space* [8]. The *Mahalanobis distance* of a point (mapping of a spectrum)  $\vec{y}$  in the *n*-dimensional principal component space to the expected value of an *n*-dimensional distribution  $\mathbf{X}$  then results as

$$d(\mathbf{X}, \vec{y}) = \sqrt{(\bar{\mathbf{X}} - \vec{y})^T \mathbf{S}^{-1} (\bar{\mathbf{X}} - \vec{y})} \quad \text{with} \quad \mathbf{X} \in \mathbb{R}^{m \times n}, \vec{y} \in \mathbb{R}^m$$

[13]. Here, *m* is equivalent to the number of principal components used (dimension of the principal component space) and *n* the number of measurements existing in the calibration data set (spectra).  $\bar{\mathbf{X}}$  is the expected value of the resulting distribution for the calibration data set (the average value of *n* measurements received).  $\mathbf{S}^{-1}$  is the inverse covariance matrix [12] for distribution  $\mathbf{X}$ .

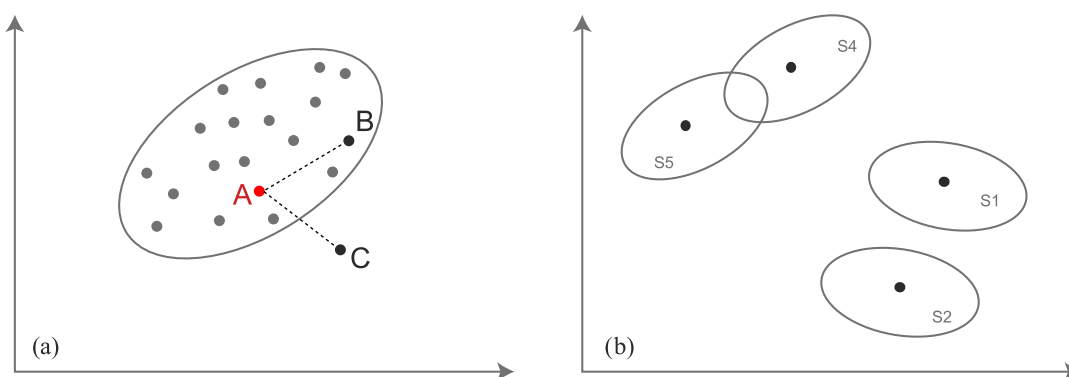


**Figure 1:** (a) The *Mahalanobis distance* from *A* to *B* is less than from *A* to *C*. However, the *Euclidean distances* are identical. (b) The *Mahalanobis distance* between the two measurement series *S4* and *S5* is smaller than between *S1* and *S2*. However, the *Euclidean distances* are identical.

The *Mahalanobis distance* offers advantages compared to the *Euclidean distance*: For the calculation of the distance it takes the statistical properties of a data point distribution (measurement series), i.e. average value, variance and covariance of the data points [14] into account. The *Mahalanobis distance* is applied while creating the reference database for evaluating the spectra from different samples of a substance.

A **chemometric model** is a classifier based on statistical methods [8, 9]. Through the respective algorithm used (e.g. *Principal Component Analysis*, *Cluster Analysis*), a maximum of chemical information is extracted from measurement data. Here, systematical or physical disturbances are eliminated using appropriate data pre-processing [15, 16].

At several places in this document, in order to simplify understanding, the term **database** is used instead of *chemometric model* – in the same manner as in the *Ph. Eur. Section 2.2.40* [3].

**As sample** applies the substance from a package. Multiple extractions of substance from the same package for spectrum recordings will be ascribed to the same sample. This also applies if multiple of such samples originate from the same batch.

Does a supplier conversely take a sample for testing from its incoming goods and splits it to multiple laboratory containers, the substance in all laboratory containers will still be ascribed to the same sample. *HiperScan GmbH* only uses one of the subsamples.

**Reference samples** are used to structure the database. The *reference spectra* originate from these samples. In chemometric technical jargon you would normally say: For *calibration*, a **chemometric model** is generated from the *calibration spectra* recorded from the *calibration samples*, whose quality is subsequently assessed in **validation**.

*Reference samples* are procured via typical pharmacy sources. Their identity is tested. The *reference spectra* are recorded by *HiperScan GmbH*. The documentation also includes the manufacturer's name and batch number.

*Reference samples* are clearly identified by a sample ID. Samples without sample ID may not be used as *reference samples*.

## Summary

A total of 287 748 spectra from 27 175 different batches for a total of 865 substances were used to validate the substance class *APIs & excipients, solid*.

### Validation samples

The validation samples can be categorised as follows:

**Type A** Calibration spectra. These are the spectra used to generate the chemometric model. They were recorded by *HiperScan GmbH*. Detailed information regarding the batches or samples can be found in the following validation reports under *calibration samples* and under *Type A*. Further information is listed in [Appendix A](#).

| Substance class            | Substances | Batches | Spectra |
|----------------------------|------------|---------|---------|
| APIs & excipients, solid   | 349        | 1464    | 65 397  |
| Specific classifier 26188  | 9          | 15      | 639     |
| Narcotic substances, solid | 17         | 73      | 5350    |

From category *A* a total of 71 386 spectra from 1552 batches for a total of 375 substances were taken into account for validation.

**Type B** Spectra from independent samples which are not included in database generation. These spectra were recorded by *HiperScan GmbH*. Detailed information regarding the batches or samples can be found in the following validation reports in the section *Type B* or in [Appendix B](#).

| Substance class            | Substances | Batches | Spectra |
|----------------------------|------------|---------|---------|
| APIs & excipients, solid   | 495        | 2077    | 90 351  |
| Narcotic substances, solid | 17         | 115     | 5210    |
| Specific classifier 26188  | 9          | 18      | 750     |
| Drugs                      | 342        | 1050    | 50 418  |

From category *B* a total of 146 729 spectra from 3260 batches for a total of 863 substances were taken into account for validation.

**Type C** Spectra from independent samples which are not included in database generation. *Apo-Ident* customers carried out the measurements. Detailed information regarding the batches or samples can be found in the following validation reports in the section *Type C* or in [Appendix C](#).

| Substance class            | Substances | Batches | Spectra |
|----------------------------|------------|---------|---------|
| APIs & excipients, solid   | 391        | 17 195  | 51 539  |
| Specific classifier 26188  | 5          | 33      | 39      |
| Narcotic substances, solid | 12         | 269     | 451     |
| Drugs                      | 289        | 6885    | 17 604  |

From category *C* a total of 69 633 spectra from 24 382 batches for a total of 697 substances were taken into account for validation.

## Validation results

The validation runs checked whether all substances/substance groups in the substance class *APIs & excipients, solid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, the matching of all relevant spectra of various substances with the substances/substance groups in the substance class *APIs & excipients, solid* was checked and the correctness of the results was evaluated. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 65 163        | 234            | 23 420 597    |
| <b>Type B</b> | 0              | 73 730        | 5595           | 48 194 065    |
| <b>Type C</b> | 0              | 46 128        | 2530           | 22 860 555    |

All substances/substance groups in the substance class *APIs & excipients, solid* can be clearly distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity                  | Recognition rate            |
|---------------|------------------------------|-----------------------------|
| <b>Type A</b> | 100.000 00 % (> 99.999 97 %) | 99.638 19 % (> 99.632 24 %) |
| <b>Type B</b> | 100.000 00 % (> 99.999 98 %) | 92.326 10 % (> 92.319 98 %) |
| <b>Type C</b> | 100.000 00 % (> 99.999 64 %) | 91.303 95 % (> 91.196 83 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Acetylcysteine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20040-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Acetylcysteine; Acetylcysteinum

### Special notes

When selecting the *Acetylcysteine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Acetylcysteine*:

| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate |
|----------|----------------|------------------|-----------|---------|-------------|
| Caelo    | Acetylcysteine | 12299020         | 21315     | 40      | 20121026    |
| Euro OTC | Acetylcysteine | 1208026-01       | 21628     | 40      | 20121116    |
| Euro OTC | Acetylcysteine | 1510016          | 22228     | 40      | 20151116*   |
| Caelo    | Acetylcysteine | 161398           | 22469     | 40      | 20160520*   |
| Euro OTC | Acetylcysteine | 1610011          | 22854     | 40      | 20161107*   |
| Fagron   | Acetylcysteine | 15C16-B06-308039 | 22886     | 40      | 20150402    |



## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Acetylcysteine*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 170 spectra of 6 reference samples from the substance/substance group *Acetylcysteine*.

| Supplier | Substance      | Batch      | Sample ID          | Spectra |
|----------|----------------|------------|--------------------|---------|
| Fagron   | Acetylcysteine | 8G23-N06   | 20040              | 30      |
| Caelo    | Acetylcysteine | 8309805    | 20176              | 40      |
| Euro OTC | Acetylcysteine | 1208026-01 | 21628 <sup>†</sup> | 20      |
| Euro OTC | Acetylcysteine | 1510016    | 22228 <sup>†</sup> | 20      |
| Caelo    | Acetylcysteine | 161398     | 22469 <sup>†</sup> | 20      |
| Caelo    | Acetylcysteine | 163340     | 23035              | 40      |

- 146 559 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 15 spectra from 13 *Apo-Ident* customers from 13 batches from the substance/substance group *Acetylcysteine*.

| Supplier                   | Substance      | Batch      | Spectra |
|----------------------------|----------------|------------|---------|
| Phönix                     | Acetylcysteine | 1208026    | 1       |
| Phoenix goettin            | Acetylcysteine | 1208026-01 | 1       |
| Euro OTC                   | Acetylcysteine | 12299010   | 1       |
| Caelo                      | Acetylcysteine | 12299021   | 1       |
| Euro OTC                   | Acetylcysteine | 1307026-02 | 1       |
| Euro OTC                   | Acetylcysteine | 1408004    | 1       |
| Caelo                      | Acetylcysteine | 15114007   | 1       |
| Sanacorp 07.03.2016 10,... | Acetylcysteine | 15114007   | 1       |
| Caelo                      | Acetylcysteine | 15114013   | 2       |
| Caelo                      | Acetylcysteine | 10230708   | 1       |
| Caelo                      | Acetylcysteine | 10230713   | 1       |
| Caelo                      | Acetylcysteine | 12299002   | 1       |
| Caelo                      | Acetylcysteine | 12299004   | 1       |
| Fagron                     | Acetylcysteine | 13A22N07   | 1       |

- 69 618 spectra from 414 *Apo-Ident* customers from a total of 23 788 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Acetylcysteine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Acetylcysteine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 157           | 13             | 146 559       |
| <b>Type C</b> | 0              | 14            | 1              | 69 618        |

The substance/substance group *Acetylcysteine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 92.3529 % (> 90.5882 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to

exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21315     | 22469               | 8.35                         | 88.22                           |
| 21628     | 22469               | 4.59                         | 86.07                           |
| 22228     | 22228               | 0.00                         | 87.07                           |
| 22469     | 22469               | 0.00                         | 84.11                           |
| 22854     | 22854               | 0.00                         | 87.33                           |
| 22886     | 22469               | 7.65                         | 87.76                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Acetylsalicylic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20449-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Acetylsalicylic acid; Acidum acetylosalicylicum; Acidum acetylsalicylicum

### Special notes

When selecting the *Acetylsalicylic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Acetylsalicylic acid*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Caelo    | Acetylsalicylic ... | 13297509   | 21383     | 40      | 20131014    |
| Euro OTC | Acetylsalicylic ... | 1307024-01 | 21597     | 40      | 20130904    |
| Euro OTC | Acetylsalicylic ... | 1407026-01 | 21637     | 40      | 20140801    |
| Euro OTC | Acetylsalicylic ... | 1601042    | 22377     | 40      | 20160204*   |
| Euro OTC | Acetylsalicylic ... | 1608037    | 22820     | 40      | 20160921*   |
| Caelo    | Acetylsalicylic ... | 161316     | 23064     | 40      | 20160825*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Acetylsalicylic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 280 spectra of 8 reference samples from the substance/substance group *Acetylsalicylic acid*.

| Supplier | Substance            | Batch            | Sample ID          | Spectra |
|----------|----------------------|------------------|--------------------|---------|
| Euro OTC | Acetylsalicylic acid | 1011015-01       | 20449              | 40      |
| Fagron   | Acetylsalicylic acid | 12D02-N01        | 20484              | 40      |
| Caelo    | Acetylsalicylic acid | 11257102         | 20508              | 40      |
| Caelo    | Acetylsalicylic acid | 11257102         | 20578              | 40      |
| Euro OTC | Acetylsalicylic acid | 1307024-01       | 21597 <sup>†</sup> | 20      |
| Euro OTC | Acetylsalicylic acid | 1407026-01       | 21637 <sup>†</sup> | 20      |
| Fagron   | Acetylsalicylic acid | 14E02-B04-297099 | 22949              | 40      |
| Euro OTC | Acetylsalicylic acid | 1703010          | 23388              | 40      |

- 146 449 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 84 spectra from 52 *Apo-Ident* customers from 44 batches from the substance/substance group *Acetylsalicylic acid*.

| Supplier  | Substance            | Batch            | Spectra |
|-----------|----------------------|------------------|---------|
| Euro OTC  | Acetylsalicylic acid | 815A-01012       | 1       |
| Caelo     | Acetylsalicylic acid | 12212223         | 4       |
| Euro OTC  | Acetylsalicylic acid | 1307024-01       | 7       |
| EuRho     | Acetylsalicylic acid | 1307024-01       | 2       |
| Caelo     | Acetylsalicylic acid | 13324109         | 2       |
| Caelo     | Acetylsalicylic acid | 13297511         | 1       |
| Phönix    | Acetylsalicylic acid | 13324114         | 1       |
| Caelo     | Acetylsalicylic acid | 13324116         | 1       |
| Euro OTC  | Acetylsalicylic acid | 1407025-01       | 11      |
| Caelo     | Acetylsalicylic acid | 14189603         | 1       |
| Caelo     | Acetylsalicylic acid | 14250101         | 1       |
| Fagron    | Acetylsalicylic acid | 14B10-B02-296841 | 1       |
| Euro OTC  | Acetylsalicylic acid | 1501046-01       | 2       |
| Caelo     | Acetylsalicylic acid | 15081301         | 1       |
| Caelo     | Acetylsalicylic acid | 15081304         | 1       |
| Caelo     | Acetylsalicylic acid | 15081310         | 1       |
| Caelo     | Acetylsalicylic acid | 15334902         | 2       |
| Caelo     | Acetylsalicylic acid | 15122701         | 1       |
| Caelo     | Acetylsalicylic acid | 15334907         | 4       |
| Caelo     | Acetylsalicylic acid | 15334910         | 1       |
| Caelo     | Acetylsalicylic acid | 15334914         | 2       |
| Noweda    | Acetylsalicylic acid | 10040403         | 1       |
| Caelo     | Acetylsalicylic acid | 15334917         | 1       |
| Caelo     | Acetylsalicylic acid | 17023102         | 1       |
| Caelo     | Acetylsalicylic acid | 10099907         | 1       |
| Gehe      | Acetylsalicylic acid | 10365302         | 1       |
| Euro OTC  | Acetylsalicylic acid | 1107007-01       | 3       |
| Caelo     | Acetylsalicylic acid | 11239703         | 1       |
| Caelo     | Acetylsalicylic acid | 11257126         | 1       |
| Caelo     | Acetylsalicylic acid | 1212005-01       | 1       |
| Euro OTC  | Acetylsalicylic acid | 1212005-01       | 2       |
| Bombastus | Acetylsalicylic acid | 1212005-01       | 1       |
| Phönix    | Acetylsalicylic acid | 12145402         | 1       |
| Caelo     | Acetylsalicylic acid | 12212203         | 1       |
| Caelo     | Acetylsalicylic acid | 12212230         | 1       |
| Caelo     | Acetylsalicylic acid | 12212219         | 1       |
| Caelo     | Acetylsalicylic acid | 12212233         | 1       |
| Caelo     | Acetylsalicylic acid | 12212234         | 2       |
| Caelo     | Acetylsalicylic acid | 12212236         | 3       |
| Sanacorp  | Acetylsalicylic acid | 1307024-01       | 1       |
| Phoenix   | Acetylsalicylic acid | 13324107         | 1       |
| Sanacorp  | Acetylsalicylic acid | 13324109         | 1       |
| Caelo     | Acetylsalicylic acid | 13324118         | 2       |
| Caelo     | Acetylsalicylic acid | 13324119         | 1       |
| Euro OTC  | Acetylsalicylic acid | 20030611-1       | 1       |
| Caelo     | Acetylsalicylic acid | 3512N-01012      | 1       |
| Noweda    | Acetylsalicylic acid | 3946120          | 1       |
| Caelo     | Acetylsalicylic acid | 15081308         | 1       |
| Euro OTC  | Acetylsalicylic acid | 1011015-01       | 1       |
| Noweda    | Acetylsalicylic acid | 1107007-01       | 1       |

- 69 549 spectra from 414 *Apo-Ident* customers from a total of 23 758 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Acetylsalicylic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Acetylsalicylic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 240           | 0              | 71 146        |
| Type B | 0              | 279           | 1              | 146 449       |
| Type C | 0              | 83            | 1              | 69 549        |

The substance/substance group *Acetylsalicylic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 99.6429 % (> 98.5714 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 98.8095 % (> 95.2381 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21383     | 22377               | 6.20                         | 54.85                           |
| 21597     | 23064               | 8.16                         | 56.48                           |
| 21637     | 22820               | 11.05                        | 50.65                           |
| 22377     | 22377               | 0.00                         | 53.82                           |
| 22820     | 22820               | 0.00                         | 51.12                           |
| 23064     | 23064               | 0.00                         | 58.07                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Labor-

prüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Aciclovir**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21677-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Aciclovir; Aciclovirum

### Special notes

When selecting the *Aciclovir* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Aciclovir*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------|------------------|-----------|---------|--------------------|
| Fagron   | Aciclovir | 13B04-B40-294559 | 21677     | 40      | AR-15-FG-002570-01 |
| Fagron   | Aciclovir | 13B04-B40-302333 | 21761     | 40      | 20131217           |
| Fagron   | Aciclovir | 14G07-B05-296462 | 21831     | 40      | 20140728           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Aciclovir*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 153 spectra of 6 reference samples from the substance/substance group *Aciclovir*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Fagron   | Aciclovir | 13B04-B40-294559 | 21677 <sup>†</sup> | 20      |
| Fagron   | Aciclovir | 13B04-B40-302333 | 21761 <sup>†</sup> | 20      |
| Fagron   | Aciclovir | 14G07-B05-296462 | 21831 <sup>†</sup> | 20      |
| Fagron   | Aciclovir | 15A15-B10-323362 | 22938              | 40      |
| Fagron   | Aciclovir | 15A15-B10-323362 | 22939              | 40      |
| Fagron   | Aciclovir | 15A15-B10-315379 | not required       | 13      |

- 146 576 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Aciclovir*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Aciclovir* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Aciclovir* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 153           | 0              | 146 576       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Aciclovir* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.0784 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21677     | 21677               | 0.00                         | 60.86                           |
| 21761     | 21677               | 5.98                         | 63.18                           |
| 21831     | 21677               | 13.29                        | 66.46                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Aescin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20377-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Aescin; Aescinum

### Special notes

When selecting the *Aescin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Aescin*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------|------------------|-----------|---------|--------------------|
| Fagron   | Aescin    | 12K22-N13        | 21237     | 30      | 20121127           |
| Euro OTC | Aescin    | 1310020-01       | 21238     | 20      | AR-15-FG-005777-01 |
| Euro OTC | Aescin    | 1506038          | 21838     | 40      | 20150708*          |
| Fagron   | Aescin    | 12I07-B40-306607 | 22610     | 40      | 1610369            |
| Euro OTC | Aescin    | 1605021          | 22684     | 40      | 20160609*          |
| Euro OTC | Aescin    | 1612012          | 22988     | 40      | 20170213*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 210 spectra of 6 reference samples from the substance/substance group *Aescin*. These samples are listed above in the [calibration samples](#) section.
- 71 176 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 170 spectra of 6 reference samples from the substance/substance group *Aescin*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Euro OTC | Aescin    | 1011033-02 | 20377              | 40      |
| Euro OTC | Aescin    | 1011033    | 20464              | 40      |
| Fagron   | Aescin    | 1011033-02 | 20580              | 40      |
| Fagron   | Aescin    | 12K22-N13  | 21237 <sup>†</sup> | 10      |
| Euro OTC | Aescin    | 1310020-01 | 21238 <sup>†</sup> | 20      |
| Euro OTC | Aescin    | 1506038    | 21838 <sup>†</sup> | 20      |

- 146 559 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Aescin*.

| Supplier | Substance | Batch      | Spectra |
|----------|-----------|------------|---------|
| Euro OTC | Aescin    | 1310020-01 | 1       |

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

### Validation results

The validation runs checked whether the substance/substance group *Aescin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Aescin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 210           | 0              | 71 176        |
| <b>Type B</b> | 0              | 142           | 28             | 146 559       |
| <b>Type C</b> | 0              | 0             | 1              | 69 632        |

The substance/substance group *Aescin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.1429 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 83.5294 % (> 81.7647 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21237     | 21238               | 10.68                        | 25.29                           |
| 21238     | 21238               | 0.00                         | 17.93                           |
| 21838     | 21838               | 0.00                         | 28.03                           |
| 22610     | 22610               | 0.00                         | 27.81                           |
| 22684     | 22684               | 0.00                         | 24.35                           |
| 22988     | 22988               | 0.00                         | 24.64                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Albendazole**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21596-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Albendazole; Albendazolum

### Special notes

When selecting the *Albendazole* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Albendazole*:

| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate        |
|----------|-------------|------------------|-----------|---------|--------------------|
| Fagron   | Albendazole | 12J25-B40-293217 | 21596     | 40      | AR-15-FG-002571-01 |
| Fagron   | Albendazole | 14B05-B41-299704 | 21730     | 40      | 20140430           |
| Fagron   | Albendazole | 16B04-B06-322057 | 22968     | 40      | 20160302           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Albendazole*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 4 reference samples from the substance/substance group *Albendazole*.

| Supplier | Substance   | Batch            | Sample ID          | Spectra |
|----------|-------------|------------------|--------------------|---------|
| Fagron   | Albendazole | 12J25-B40-293217 | 21596 <sup>†</sup> | 20      |
| Fagron   | Albendazole | 14B05-B41-299704 | 21730 <sup>†</sup> | 20      |
| Fagron   | Albendazole | 14B05-B41-314321 | 22940              | 40      |
| Fagron   | Albendazole | 16B04-B06-329519 | 23017              | 40      |

- 146 609 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 4 spectra from 4 *Apo-Ident* customers from 4 batches from the substance/substance group *Albendazole*.

| Supplier | Substance   | Batch     | Spectra |
|----------|-------------|-----------|---------|
| Fagron   | Albendazole | 14B05-B41 | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier | Substance   | Batch            | Spectra |
|----------|-------------|------------------|---------|
| Fagron   | Albendazole | 14B05B41-312959  | 1       |
| Fagron   | Albendazole | 14b05-b41-314321 | 1       |
| Fagron   | Albendazole | 14B05-B41-314321 | 1       |

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Albendazole* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Albendazole* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 120           | 0              | 146 609       |
| <b>Type C</b> | 0              | 4             | 0              | 69 629        |

The substance/substance group *Albendazole* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21596     | 21596               | 0.00                         | 69.28                           |
| 21730     | 21596               | 12.80                        | 68.54                           |
| 22968     | 21596               | 11.58                        | 66.51                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Alfatradiol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20292-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Alfatradiol; 17-alpha-Estradiolum; Alfatradiolum

### Special notes

When selecting the *Alfatradiol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Alfatradiol*:

| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate |
|----------|-------------|------------------|-----------|---------|-------------|
| Fagron   | Alfatradiol | 13G19-N06        | 20940     | 40      | 1402683     |
| Caelo    | Alfatradiol | 13201601         | 21476     | 80      | 20130812    |
| Euro OTC | Alfatradiol | 1404001-01       | 21714     | 40      | 1509288     |
| Euro OTC | Alfatradiol | 1603019          | 22511     | 40      | 20160419*   |
| Fagron   | Alfatradiol | 15J27-B08-323877 | 22934     | 40      | 20151117    |

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| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate |
|----------|-------------|------------------|-----------|---------|-------------|
| Euro OTC | Alfatradiol | 1404001-01       | 21714SI   | 40      | 1509288     |
| Euro OTC | Alfatradiol | 1603019          | 22511SI   | 40      | 20160419*   |
| Fagron   | Alfatradiol | 15J27-B08-323877 | 22934SI   | 40      | 20151117    |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 360 spectra of 8 reference samples from the substance/substance group *Alfatradiol*. These samples are listed above in the [calibration samples](#) section.
- 71 026 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 550 spectra of 14 reference samples from the substance/substance group *Alfatradiol*.

| Supplier     | Substance   | Batch              | Sample ID            | Spectra |
|--------------|-------------|--------------------|----------------------|---------|
| Fagron       | Alfatradiol | 11B07-N05          | 20194                | 40      |
| Caelo        | Alfatradiol | 11061005           | 20292                | 40      |
| Fagron       | Alfatradiol | 11G22-N11          | 20545                | 40      |
| Caelo        | Alfatradiol | 13201601           | 21476 <sup>†</sup>   | 40      |
| Caelo        | Alfatradiol | 13201601           | 21477                | 60      |
| Euro OTC     | Alfatradiol | 1404001-01         | 21714 <sup>†</sup>   | 10      |
| Fagron       | Alfatradiol | 15J27-B08-323877   | 22933                | 40      |
| Audor Pharma | Alfatradiol | AP33-16-I-62P2985A | 22935                | 40      |
| Caelo        | Alfatradiol | 161804             | 23354                | 40      |
| Caelo        | Alfatradiol | 13201601           | 21477SI              | 60      |
| Euro OTC     | Alfatradiol | 1404001-01         | 21714SI <sup>†</sup> | 20      |
| Fagron       | Alfatradiol | 15J27-B08-323877   | 22933SI              | 40      |
| Audor Pharma | Alfatradiol | AP33-16-I-62P2985A | 22935SI              | 40      |
| Caelo        | Alfatradiol | 161804             | 23354SI              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 179 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 245 spectra from 108 *Apo-Ident* customers from 96 batches from the substance/substance group *Alfatradiol*.

| Supplier                  | Substance   | Batch            | Spectra |
|---------------------------|-------------|------------------|---------|
| VDL 1.7.14;40.30 euro     | Alfatradiol | 13G19-N06        | 1       |
| Fagron                    | Alfatradiol | 12H29-N05        | 6       |
| Caelo                     | Alfatradiol | 13130805         | 6       |
| Fagron                    | Alfatradiol | 14C20-B02-294944 | 2       |
| Audor Pharma              | Alfatradiol | APXPC0071A       | 3       |
| Fagron                    | Alfatradiol | 12L19-N08        | 8       |
| Caelo                     | Alfatradiol | 13201605         | 7       |
| Fagron                    | Alfatradiol | 13G19-N06        | 21      |
| Audor Pharma              | Alfatradiol | APXP103DAA       | 2       |
| Caelo                     | Alfatradiol | 2061504          | 1       |
| Caelo                     | Alfatradiol | 5051406          | 1       |
| Fagron                    | Alfatradiol | 12J27-B08-314546 | 1       |
| Sanacorp                  | Alfatradiol | 13201605         | 1       |
| Fagron                    | Alfatradiol | 13201605         | 1       |
| Fagron                    | Alfatradiol |                  | 1       |
| Fagron                    | Alfatradiol | 13L30-B32        | 3       |
| Fagron                    | Alfatradiol | 13L30B32         | 1       |
| Fagron                    | Alfatradiol | 13L30-B32-290739 | 1       |
| Fagron                    | Alfatradiol | 13L30-B32-290742 | 1       |
| Fagron                    | Alfatradiol | 13130b32290742   | 1       |
| Fagron                    | Alfatradiol | 14/22-B30-302017 | 1       |
| Caelo                     | Alfatradiol | 14037904         | 3       |
| Caelo                     | Alfatradiol | 14130104         | 1       |
| Caelo                     | Alfatradiol | 14139102         | 2       |
| Caelo                     | Alfatradiol | 14139103         | 6       |
| Caelo                     | Alfatradiol | 14139104         | 9       |
| Caelo                     | Alfatradiol | 14139105         | 1       |
| Fagron                    | Alfatradiol | 1422B30302019    | 1       |
| Caelo                     | Alfatradiol | 14318502         | 1       |
| Caelo                     | Alfatradiol | 14318512         | 1       |
| Fagron                    | Alfatradiol | 14722-B30-302018 | 1       |
| Fagron                    | Alfatradiol | 14C20-B02-294943 | 1       |
| Caelo                     | Alfatradiol | 14C20-B02-294943 | 2       |
| Fagron                    | Alfatradiol | 14G07-B99-294942 | 1       |
| Fagron                    | Alfatradiol | 14G07-B99        | 1       |
| Fagron                    | Alfatradiol | 14G07-B99-294945 | 4       |
| Caelo                     | Alfatradiol | 14C20-B02-294944 | 1       |
| Caelo                     | Alfatradiol | 14I22-B30-302019 | 1       |
| Fagron                    | Alfatradiol | 14I22-B30-302017 | 1       |
| Caelo                     | Alfatradiol | 15356801         | 7       |
| Sanacorp;21.7.15;42,35EUR | Alfatradiol | 14122-B30-302018 | 1       |
| Phönix                    | Alfatradiol | 15356801         | 1       |

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| Supplier                    | Substance   | Batch              | Spectra |
|-----------------------------|-------------|--------------------|---------|
| Caelo                       | Alfatradiol | 15356804           | 2       |
| Caelo                       | Alfatradiol | 1536801            | 1       |
| Caelo                       | Alfatradiol | 15380001           | 7       |
| Fagron                      | Alfatradiol | 15G07-B01          | 1       |
| Fagron                      | Alfatradiol | 15G07-B01-310227   | 3       |
| Caelo                       | Alfatradiol | 15G07-B01-310227   | 1       |
| Fagron                      | Alfatradiol | 15G07-B01-310228   | 1       |
| Fagron                      | Alfatradiol | 15G07-B01-310229   | 3       |
| Fagron                      | Alfatradiol | 15G07-B01-311881   | 1       |
| Caelo                       | Alfatradiol | 15G07-B01-311881   | 1       |
| Fagron                      | Alfatradiol | 15J27-B08          | 3       |
| Fagron                      | Alfatradiol | 15j27-B08-314546   | 1       |
| Fagron                      | Alfatradiol | 15J27B08318164     | 1       |
| Fagron                      | Alfatradiol | 15J27-B08-318783   | 1       |
| Fagron                      | Alfatradiol | 15J27-B08-321786   | 1       |
| Gehe                        | Alfatradiol | 16087501           | 1       |
| Caelo                       | Alfatradiol | 16087501           | 1       |
| Fagron                      | Alfatradiol | 5102423            | 1       |
| Shandong northwest manu...  | Alfatradiol | AEC151211          | 1       |
| Sanacorp, 39,57EUR, 27.1.17 | Alfatradiol | 700670-0011        | 1       |
| Shandong Northwest Manu...  | Alfatradiol | AEC160522          | 1       |
| Audor Pharma                | Alfatradiol | AP1404001-01A      | 1       |
| Audor Pharma                | Alfatradiol | AP1504015-01A      | 3       |
| Audor Pharma                | Alfatradiol | AP33-16-I-42P2945A | 1       |
| Audor Pharma                | Alfatradiol | AP5100461A         | 5       |
| Audor Pharma                | Alfatradiol | APXPC0071          | 1       |
| Phönix                      | Alfatradiol | APXPC0071A         | 1       |
| Audor Pharma                | Alfatradiol | AP3316I62P2985A    | 1       |
| Audor Pharma                | Alfatradiol | AP33-16-I-62P2985A | 1       |
| Audor Pharma                | Alfatradiol | AP5104925A         | 4       |
| Sanacorp                    | Alfatradiol | AP5104925A         | 1       |
| Caelo                       | Alfatradiol | 511211             | 1       |
| Audor Pharma                | Alfatradiol | AP514925A          | 1       |
| Caelo                       | Alfatradiol | 10319904           | 1       |
| carlo                       | Alfatradiol | 10319903           | 1       |
| Caelo                       | Alfatradiol | 10319909           | 1       |
| Caelo                       | Alfatradiol | 111161607          | 1       |
| Caesar/Lorenz               | Alfatradiol | 11061001           | 1       |
| Caelo                       | Alfatradiol | 11061001           | 2       |
| Caelo                       | Alfatradiol | 11161805           | 6       |
| Caelo                       | Alfatradiol | 11161807           | 4       |
| Fagron                      | Alfatradiol | 11B07-N05          | 1       |
| Fagron                      | Alfatradiol | 11D07-N19          | 1       |
| Fagron                      | Alfatradiol | 11G22-N11          | 3       |
| Fagron                      | Alfatradiol | 11K25-N01          | 3       |
| Fagron                      | Alfatradiol | 11k25-N01          | 1       |
| Caelo                       | Alfatradiol | 12164201           | 5       |
| Großhandel                  | Alfatradiol | 12164201           | 1       |
| Caelo                       | Alfatradiol | 12164207           | 9       |
| Caesar&Loretz GmbH/Anzag    | Alfatradiol | 12164207           | 1       |
| Euro OTC                    | Alfatradiol | 121696             | 1       |
| Noweda                      | Alfatradiol | 12D19-N03          | 2       |
| Fagron                      | Alfatradiol | 12D19-N03          | 6       |
| Phoenix                     | Alfatradiol | 12D19-N03          | 1       |
| Caelo                       | Alfatradiol | 12H29N05           | 1       |
| Fagron                      | Alfatradiol | 12L10-N08          | 1       |
| Hirsch                      | Alfatradiol | 12L19-N08          | 2       |
| Fagron                      | Alfatradiol | 12L19-No8          | 1       |
| Caelo                       | Alfatradiol | 13130806           | 2       |
| Caelo                       | Alfatradiol | 13130808           | 4       |

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| Supplier     | Substance   | Batch           | Spectra |
|--------------|-------------|-----------------|---------|
| Fagron       | Alfatradiol | 13G19-N06       | 1       |
| Fagron       | Alfatradiol | 13G19-N09       | 1       |
| Fagron       | Alfatradiol | 13G19-No6       | 1       |
| Fagron       | Alfatradiol | 13L30B32-290741 | 1       |
| Audor Pharma | Alfatradiol | AP9374-2/10A    | 1       |
| Audor Pharma | Alfatradiol | AP9374-3/11A    | 1       |
| Audor Pharma | Alfatradiol | ap9374311a      | 1       |
| Fagron       | Alfatradiol | XP101UT         | 1       |
| Audor Pharma | Alfatradiol | XP103DAA        | 1       |
| Caelo        | Alfatradiol | 11061004        | 1       |

- 69 388 spectra from 414 *Apo-Ident* customers from a total of 23 706 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Alfatradiol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Alfatradiol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 360           | 0              | 71 026        |
| <b>Type B</b> | 0              | 550           | 0              | 146 179       |
| <b>Type C</b> | 0              | 226           | 19             | 69 388        |

The substance/substance group *Alfatradiol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.3333 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.9091 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 92.2449 % (> 91.0204 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20940     | 20940               | 0.00                         | 27.75                           |
| 21476     | 22511               | 5.50                         | 29.22                           |
| 21714     | 21714               | 0.00                         | 27.54                           |
| 22511     | 22511               | 0.00                         | 27.34                           |
| 22934     | 22511               | 2.89                         | 27.43                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Allantoin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20079-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Allantoin; Allantoinum

### Special notes

When selecting the *Allantoin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Allantoin*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Fagron   | Allantoin | 13I03-B05  | 21216     | 40      | 20130927    |
| Euro OTC | Allantoin | 1406011-01 | 21625     | 40      | 20140718    |
| Euro OTC | Allantoin | 1609012    | 22750     | 40      | 20161006*   |
| Euro OTC | Allantoin | 1609012-01 | 22810     | 40      | 20161006    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Allantoin*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Allantoin*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Caelo    | Allantoin | 91749379   | 20079              | 40      |
| Euro OTC | Allantoin | 1406011-01 | 21625 <sup>†</sup> | 20      |
| Caelo    | Allantoin | 162289     | 22756              | 40      |
| Caelo    | Allantoin | 172346     | 23629              | 40      |
| Caelo    | Allantoin | 172346     | 23635              | 40      |

- 146 549 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 277 spectra from 96 *Apo-Ident* customers from 76 batches from the substance/substance group *Allantoin*.

| Supplier                   | Substance | Batch       | Spectra |
|----------------------------|-----------|-------------|---------|
| Caelo                      | Allantoin | 2264594     | 1       |
| Caelo                      | Allantoin | 3091301     | 1       |
| Caelo                      | Allantoin | 5051402     | 1       |
| Caelo                      | Allantoin | 10064012    | 1       |
| Caelo                      | Allantoin | 10064008    | 1       |
| Caelo                      | Allantoin | 10064015    | 1       |
| Caelo                      | Allantoin | 10318304    | 2       |
| Caelo                      | Allantoin | 10318305    | 1       |
| Caelo                      | Allantoin | 10318313    | 2       |
| Caelo                      | Allantoin | 10318312    | 1       |
| Caelo                      | Allantoin | 1113E-01087 | 1       |
| Anzag                      | Allantoin | 10318315    | 1       |
| Caelo                      | Allantoin | 11247504    | 7       |
| Caelo                      | Allantoin | 11247510    | 5       |
| Caelo                      | Allantoin | 11247511    | 2       |
| Noweda                     | Allantoin | 11J11-N11   | 1       |
| Fagron                     | Allantoin | 11J11-N11   | 3       |
| Caelo                      | Allantoin | 1225101     | 1       |
| Caelo                      | Allantoin | 12251501    | 6       |
| Anzag                      | Allantoin | 12251501    | 1       |
| Sanacorp                   | Allantoin | 12251501    | 1       |
| Caelo                      | Allantoin | 12251502    | 2       |
| Caelo                      | Allantoin | 12251505    | 10      |
| Caesar & Loretz GmbH       | Allantoin | 12251505    | 1       |
| DSM Nutritional Prod./ ... | Allantoin | 12251505    | 1       |
| Caelo                      | Allantoin | 12251509    | 1       |
| Caelo                      | Allantoin | 12251510    | 11      |
| Caesar & Loretz GmbH       | Allantoin | 12251510    | 1       |
| Sanacorp                   | Allantoin | 12251510    | 1       |
| Gehe                       | Allantoin | 12251510    | 1       |
| Caesar & Loretz GmbH       | Allantoin | 12374403    | 1       |
| Caelo                      | Allantoin | 12374403    | 8       |
| celo/Jenne                 | Allantoin | 12374403    | 1       |
| Caelo                      | Allantoin | 12374404    | 2       |
| Caelo                      | Allantoin | 12374407    | 6       |
| Caelo                      | Allantoin | 12374408    | 1       |
| Sanacorp                   | Allantoin | 12374409    | 2       |
| Caelo                      | Allantoin | 12374409    | 17      |
| Caesar & Loretz GmbH       | Allantoin | 12374409    | 1       |
| Caesar&Loretz GmbH         | Allantoin | 12374409    | 1       |
| Caelo                      | Allantoin | 12374414    | 9       |
| Caelo                      | Allantoin | 12374415    | 12      |
| Caesar & Loretz GmbH       | Allantoin | 12374415    | 1       |
| Caesar & Loretz GmbH       | Allantoin | 12374416    | 1       |
| Caelo                      | Allantoin | 12374417    | 1       |
| Caelo                      | Allantoin | 12374418    | 2       |
| Caelo                      | Allantoin | 12374422    | 7       |
| Sanacorp                   | Allantoin | 12374422    | 1       |
| Caelo                      | Allantoin | 12374423    | 4       |
| Noweda                     | Allantoin | 12B09-N08   | 2       |
| Fagron                     | Allantoin | 12B09-N09   | 1       |
| Caelo                      | Allantoin | 12bo9-no8   | 1       |
| Fagron                     | Allantoin | 12C30-N04   | 2       |
| Noweda                     | Allantoin | 13A21-N07   | 2       |
| Fagron                     | Allantoin | 13A21-N07   | 3       |
| Fagron                     | Allantoin | 13G16-N07   | 8       |
| Fargron/AHD                | Allantoin | 13G16-N07   | 1       |

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| Supplier               | Substance | Batch            | Spectra |
|------------------------|-----------|------------------|---------|
| Fagron                 | Allantoin | 13I03-B05-289430 | 1       |
| Euro OTC               | Allantoin | 1401046-01       | 4       |
| Phoenix 08.10.14       | Allantoin | 1401046-01       | 1       |
| Euro OTC               | Allantoin | 140104601        | 1       |
| Caelo                  | Allantoin | 140512           | 1       |
| Euro OTC               | Allantoin | 1406011-01       | 7       |
| Euro OTC               | Allantoin | 1406011-02       | 1       |
| Euro OTC               | Allantoin | 140601103        | 1       |
| Caelo                  | Allantoin | 14247602         | 8       |
| Caesar & Loretz GmbH   | Allantoin | 14247602         | 1       |
| Gehe                   | Allantoin | 14247603         | 1       |
| Caelo                  | Allantoin | 14247609         | 6       |
| Caelo                  | Allantoin | 152200012        | 1       |
| Caelo                  | Allantoin | 15220004         | 3       |
| Caelo                  | Allantoin | 15220005         | 2       |
| Caelo                  | Allantoin | 15220006         | 13      |
| Caelo                  | Allantoin | 15220007         | 6       |
| Caelo                  | Allantoin | 15220008         | 7       |
| Caelo                  | Allantoin | 15220010         | 2       |
| Caelo                  | Allantoin | 15220011         | 2       |
| Caelo                  | Allantoin | 15220012         | 7       |
| Caelo                  | Allantoin | 15275302         | 1       |
| Caelo                  | Allantoin | 15275305         | 1       |
| Caelo                  | Allantoin | 15275312         | 1       |
| AHD                    | Allantoin | 1609012-01       | 1       |
| Caelo                  | Allantoin | 16228903         | 5       |
| Fagron                 | Allantoin | 16228903         | 1       |
| Caelo                  | Allantoin | 20071202         | 1       |
| Caelo                  | Allantoin | 20140612-15      | 1       |
| Caelo                  | Allantoin | 24061401         | 1       |
| Caelo                  | Allantoin | 2713431          | 1       |
| Caelo                  | Allantoin | 2713448          | 1       |
| Fagron                 | Allantoin | 5011E-01087      | 1       |
| Caelo                  | Allantoin | 81542358         | 4       |
| Fagron                 | Allantoin | K93403115        | 1       |
| VDL 17.10.14           | Allantoin | 12374415         | 2       |
| Caelo                  | Allantoin | 12374416         | 1       |
| Anzag;18.03.15;2,76EUR | Allantoin | 14247602         | 2       |
| AHD                    | Allantoin | 14247603         | 3       |
| Caelo                  | Allantoin | 10318306         | 1       |
| Caelo                  | Allantoin | 12374401         | 1       |
| Caelo                  | Allantoin | 12251511         | 1       |
| Caelo                  | Allantoin | 4908E-01087      | 1       |

- 69 356 spectra from 414 *Apo-Ident* customers from a total of 23 726 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Allantoin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Allantoin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table

breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 148           | 32             | 146 549       |
| <b>Type C</b> | 0              | 262           | 15             | 69 356        |

The substance/substance group *Allantoin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 82.2222 % (> 80.5556 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 94.5848 % (> 93.5018 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21216     | 22750               | 9.54                         | 43.85                           |
| 21625     | 22750               | 8.55                         | 43.42                           |
| 22750     | 22750               | 0.00                         | 43.22                           |
| 22810     | 22750               | 5.42                         | 44.12                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Allopurinol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22243-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Allopurinol; Allopurinolum

### Special notes

When selecting the *Allopurinol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Allopurinol*:

| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate        |
|----------|-------------|------------------|-----------|---------|--------------------|
| Fagron   | Allopurinol | 14E15-B05-307746 | 22243     | 40      | AR-16-FG-004367-01 |
| Fagron   | Allopurinol | 14E15-B05-315557 | 22345     | 40      | 20140611           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Allopurinol*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 173 spectra of 6 reference samples from the substance/substance group *Allopurinol*.

| Supplier | Substance   | Batch            | Sample ID          | Spectra |
|----------|-------------|------------------|--------------------|---------|
| Fagron   | Allopurinol | 14E15-B05-307746 | 22243 <sup>†</sup> | 20      |
| Fagron   | Allopurinol | 14E15-B05-315557 | 22345 <sup>†</sup> | 20      |
| Fagron   | Allopurinol | 14E15-B05-307746 | 22836              | 40      |
| Fagron   | Allopurinol | 14E15-B05-330859 | 23523              | 40      |
| Fagron   | Allopurinol | 14E15-B05-330859 | 23526              | 40      |
| Fagron   | Allopurinol | 14E15-B05-315557 | not required       | 13      |

- 146 556 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Allopurinol*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Allopurinol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Allopurinol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 173           | 0              | 146 556       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Allopurinol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.5318 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22243     | 22243               | 0.00                         | 91.56                           |
| 22345     | 22243               | 2.64                         | 89.52                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **alpha-tocopheryl acetate dry concentrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20433-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

alpha-tocopheryl acetate dry concentrate; alpha-Tocopheroli acetas pulvis; alpha-Tocopherolum aceticum siccatum

### Special notes

When selecting the *alpha-tocopheryl acetate dry concentrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *alpha-tocopheryl acetate dry concentrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Euro OTC | alpha-tocopheryl... | 1110021-02       | 20907     | 40      | 20120104           |
| Fagron   | alpha-tocopheryl... | 13H30-B02-287169 | 21609     | 40      | AR-15-FG-006388-01 |
| Euro OTC | alpha-tocopheryl... | 1305032-01       | 21680     | 40      | AR-15-FG-001194-01 |
| Euro OTC | alpha-tocopheryl... | 1507001          | 21842     | 40      | 20130708*          |
| Fagron   | alpha-tocopheryl... | 14B03-B04-295113 | 21959     | 40      | 20140224           |
| Euro OTC | alpha-tocopheryl... | 1603046          | 22543     | 40      | 20160429*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *alpha-tocopheryl acetate dry concentrate*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 7 reference samples from the substance/substance group *alpha-tocopheryl acetate dry concentrate*.

| Supplier                   | Substance                       | Batch            | Sample ID          | Spectra |
|----------------------------|---------------------------------|------------------|--------------------|---------|
| Bulk Medicines & Pharma... | alpha-tocopheryl acetate dry... | 2009060301       | 20433              | 40      |
| Fagron                     | alpha-tocopheryl acetate dry... | 13H30-B02-287169 | 21609 <sup>†</sup> | 20      |
| Euro OTC                   | alpha-tocopheryl acetate dry... | 1305032-01       | 21680 <sup>†</sup> | 20      |
| Euro OTC                   | alpha-tocopheryl acetate dry... | 1507001          | 21842 <sup>†</sup> | 20      |
| Fagron                     | alpha-tocopheryl acetate dry... | 14B03-B04-295113 | 21959 <sup>†</sup> | 20      |
| Fagron                     | alpha-tocopheryl acetate dry... | 16H30-B05-326792 | 22948              | 40      |
| Euro OTC                   | alpha-tocopheryl acetate dry... | 1705003          | 23424              | 40      |

- 146 529 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 19 spectra from 5 *Apo-Ident* customers from 12 batches from the substance/substance group *alpha-tocopheryl acetate dry concentrate*.

| Supplier      | Substance                       | Batch            | Spectra |
|---------------|---------------------------------|------------------|---------|
| Euro OTC      | alpha-tocopheryl acetate dry... | 1110021-02       | 2       |
| Euro OTC      | alpha-tocopheryl acetate dry... | 1305032-02       | 1       |
| Euro OTC      | alpha-tocopheryl acetate dry... | 1305032-01       | 2       |
| Fagron        | alpha-tocopheryl acetate dry... | 13H30-B02-287169 | 1       |
| Euro OTC      | alpha-tocopheryl acetate dry... | 1406013-01       | 3       |
| Euro OTC      | alpha-tocopheryl acetate dry... | 1406013-03       | 3       |
| Euro OTC      | alpha-tocopheryl acetate dry... | 1507001-01       | 2       |
| Euro/Sanacorp | alpha-tocopheryl acetate dry... | 150700101        | 1       |
| Bombastus     | alpha-tocopheryl acetate dry... | 1507001-02       | 1       |
| Euro OTC      | alpha-tocopheryl acetate dry... | 7120             | 1       |
| Euro OTC      | alpha-tocopheryl acetate dry... | 1110021-01       | 1       |
| BMP           | alpha-tocopheryl acetate dry... | 2011052301       | 1       |

- 69 614 spectra from 414 *Apo-Ident* customers from a total of 23 790 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *alpha-tocopheryl acetate dry concentrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *alpha-tocopheryl acetate dry concentrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 160           | 40             | 146 529       |
| <b>Type C</b> | 0              | 15            | 4              | 69 614        |

The substance/substance group *alpha-tocopheryl acetate dry concentrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 80.0000 % (> 78.5000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to

exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20907     | 21680               | 4.82                         | 41.31                           |
| 21609     | 21609               | 0.00                         | 44.49                           |
| 21680     | 21680               | 0.00                         | 41.08                           |
| 21842     | 21842               | 0.00                         | 44.12                           |
| 21959     | 21680               | 4.79                         | 41.38                           |
| 22543     | 22543               | 0.00                         | 44.09                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ambroxol hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20742-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ambroxol hydrochloride; Ambroxoli hydrochloridum; Ambroxolum hydrochloricum

### Special notes

When selecting the *Ambroxol hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ambroxol hydrochloride*:

| Supplier | Substance             | Batch       | Sample ID | Spectra | Certificate |
|----------|-----------------------|-------------|-----------|---------|-------------|
| Euro OTC | Ambroxol hydroch. ... | 11110008-01 | 20742     | 40      | 1401146     |
| Fagron   | Ambroxol hydroch. ... | 13I24-N02   | 21230     | 40      | 20131017    |
| Euro OTC | Ambroxol hydroch. ... | 1311032-01  | 21244     | 40      | 20131219    |
| Euro OTC | Ambroxol hydroch. ... | 1509032     | 21942     | 40      | 20151027*   |
| Euro OTC | Ambroxol hydroch. ... | 1601008     | 22298     | 40      | 20160119*   |
| Euro OTC | Ambroxol hydroch. ... | 1602015     | 22347     | 40      | 20160217*   |
| Euro OTC | Ambroxol hydroch. ... | 1604035     | 22550     | 40      | 20160428*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 280 spectra of 7 reference samples from the substance/substance group *Ambroxol hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 106 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 7 reference samples from the substance/substance group *Ambroxol hydrochloride*.

| Supplier | Substance              | Batch   | Sample ID          | Spectra |
|----------|------------------------|---------|--------------------|---------|
| Euro OTC | Ambroxol hydrochloride | 1509032 | 21942 <sup>†</sup> | 20      |
| Euro OTC | Ambroxol hydrochloride | 1601008 | 22298 <sup>†</sup> | 20      |
| Euro OTC | Ambroxol hydrochloride | 1602015 | 22347 <sup>†</sup> | 20      |
| Caelo    | Ambroxol hydrochloride | 161996  | 22636              | 40      |
| Euro OTC | Ambroxol hydrochloride | 1609002 | 22800              | 40      |
| Euro OTC | Ambroxol hydrochloride | 1702004 | 23155              | 40      |
| Caelo    | Ambroxol hydrochloride | 171582  | 23344              | 40      |

- 146 509 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 24 spectra from 16 *Apo-Ident* customers from 13 batches from the substance/substance group *Ambroxol hydrochloride*.

| Supplier      | Substance              | Batch            | Spectra |
|---------------|------------------------|------------------|---------|
| Euro OTC      | Ambroxol hydrochloride | 1311032-01       | 1       |
| Euro/Noweda   | Ambroxol hydrochloride | 1509032-01       | 1       |
| EuroTOC       | Ambroxol hydrochloride | 1602015-01       | 1       |
| Fagron        | Ambroxol hydrochloride | 1602015-01       | 1       |
| Caelo         | Ambroxol hydrochloride | 1602015-02       | 1       |
| Euro OTC      | Ambroxol hydrochloride | 1602015-02       | 1       |
| Euro OTC      | Ambroxol hydrochloride | 1604031-01       | 1       |
| Euro OTC      | Ambroxol hydrochloride | 1604032-01       | 1       |
| Euro OTC      | Ambroxol hydrochloride | 1604035-01       | 1       |
| Phoenix       | Ambroxol hydrochloride | 1604035-02       | 1       |
| Euro OTC      | Ambroxol hydrochloride | 1604035-02       | 3       |
| Sanacorp      | Ambroxol hydrochloride | 1604035-02       | 1       |
| Caelo         | Ambroxol hydrochloride | 1609002-01       | 3       |
| Euro OTC      | Ambroxol hydrochloride | 1609002-01       | 1       |
| Caelo         | Ambroxol hydrochloride | 16199603         | 2       |
| Fagron        | Ambroxol hydrochloride | 16G12-B06-326184 | 1       |
| Chem & Pharma | Ambroxol hydrochloride | AXL0361201310    | 1       |
| Caelo         | Ambroxol hydrochloride | 1604035-01       | 1       |
| Fagron        | Ambroxol hydrochloride | 12K12-N02        | 1       |

- 69 609 spectra from 414 *Apo-Ident* customers from a total of 23 789 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ambroxol hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ambroxol hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 280           | 0              | 71 106        |
| <b>Type B</b> | 0              | 220           | 0              | 146 509       |
| <b>Type C</b> | 0              | 24            | 0              | 69 609        |

The substance/substance group *Ambroxol hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.8571 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.2727 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 75.0000 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several

new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20742     | 20742               | 0.00                         | 40.73                           |
| 21230     | 22347               | 3.22                         | 40.86                           |
| 21244     | 22347               | 3.06                         | 40.53                           |
| 21942     | 21942               | 0.00                         | 42.19                           |
| 22298     | 22298               | 0.00                         | 40.66                           |
| 22347     | 22347               | 0.00                         | 40.19                           |
| 22550     | 22550               | 0.00                         | 41.08                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Amiloride hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21879-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Amiloride hydrochloride; Amiloridi hydrochloridum dihydricum; Amiloridum hydrochloricum dihydricum

### Special notes

When selecting the *Amiloride hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Amiloride hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Amiloride hydroc... | 13J08-B04-288620 | 21879     | 40      | AR-16-FG-008919-01 |
| Fagron   | Amiloride hydroc... | 13J08-B04-304547 | 22339     | 40      | 20131024           |
| Fagron   | Amiloride hydroc... | 16K07-B02-329114 | 23119     | 40      | 20170104           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Amiloride hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 4 reference samples from the substance/substance group *Amiloride hydrochloride*.

| Supplier | Substance               | Batch            | Sample ID          | Spectra |
|----------|-------------------------|------------------|--------------------|---------|
| Fagron   | Amiloride hydrochloride | 13J08-B04-288620 | 21879 <sup>†</sup> | 20      |
| Fagron   | Amiloride hydrochloride | 13J08-B04-304547 | 22339 <sup>†</sup> | 20      |
| Fagron   | Amiloride hydrochloride | 15C25-B05-325653 | 22834              | 40      |
| Fagron   | Amiloride hydrochloride | 17F02-B06-335953 | 23525              | 40      |

- 146 609 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Amiloride hydrochloride*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier         | Substance               | Batch     | Spectra |
|------------------|-------------------------|-----------|---------|
| Ebert 04.04.2014 | Amiloride hydrochloride | 13J08-B04 | 1       |

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Amiloride hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Amiloride hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 114           | 6              | 146 609       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Amiloride hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 95.0000 % (> 92.5000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21879     | 21879               | 0.00                         | 48.89                           |
| 22339     | 21879               | 7.10                         | 43.95                           |
| 23119     | 21879               | 15.03                        | 46.27                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Amitriptyline hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22844-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Amitriptyline hydrochloride; Amitriptylini hydrochloridum; Amitriptylinum hydrochloricum

### Special notes

When selecting the *Amitriptyline hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Amitriptyline hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Amitriptyline hy... | 16C31-B01-325540 | 22844     | 40      | 20160425    |
| Inresa   | Amitriptyline hy... | 005669/17112016  | 22845     | 40      | 1705099     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Amitriptyline hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *Amitriptyline hydrochloride*.

| Supplier | Substance                   | Batch            | Sample ID | Spectra |
|----------|-----------------------------|------------------|-----------|---------|
| Inresa   | Amitriptyline hydrochloride | 5669/06022017    | 23078     | 40      |
| Fagron   | Amitriptyline hydrochloride | 17E11-B02-335098 | 23528     | 40      |

- 146 649 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Amitriptyline hydrochloride*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Amitriptyline hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Amitriptyline hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Amitriptyline hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22844     | 22845               | 14.24                        | 69.69                           |
| 22845     | 22845               | 0.00                         | 68.30                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Amphotericin B**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20933-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Amphotericin B; Amphotericinum B

### Special notes

When selecting the *Amphotericin B* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Amphotericin B*:

| Supplier | Substance      | Batch      | Sample ID | Spectra | Certificate |
|----------|----------------|------------|-----------|---------|-------------|
| Euro OTC | Amphotericin B | 1305033-02 | 20933     | 40      | 1403224     |
| Fagron   | Amphotericin B | 13I16-N02  | 21338     | 40      | 1508271     |
| Fagron   | Amphotericin B | 13I16-N02  | 21951     | 40      | 20130911    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Amphotericin B*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 112 spectra of 4 reference samples from the substance/substance group *Amphotericin B*.

| Supplier | Substance      | Batch            | Sample ID          | Spectra |
|----------|----------------|------------------|--------------------|---------|
| Fagron   | Amphotericin B | 13I16-N02        | 21951 <sup>†</sup> | 20      |
| Euro OTC | Amphotericin B | 1512026-01       | 22813              | 40      |
| Fagron   | Amphotericin B | 16L06-B04-333234 | 23530              | 40      |
| Euro OTC | Amphotericin B | 1305033-03       | not required       | 12      |

- 146 617 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 3 spectra from 2 *Apo-Ident* customers from 2 batches from the substance/substance group *Amphotericin B*.

| Supplier | Substance      | Batch      | Spectra |
|----------|----------------|------------|---------|
| Euro OTC | Amphotericin B | 1512026-01 | 2       |
| Fagron   | Amphotericin B | 5173       | 1       |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 630 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Amphotericin B* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Amphotericin B* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 112           | 0              | 146 617       |
| <b>Type C</b> | 0              | 3             | 0              | 69 630        |

The substance/substance group *Amphotericin B* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.6429 %) |
| <b>Type C</b> | 100.0000 % (> 99.8817 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20933     | 20933               | 0.00                         | 18.83                           |
| 21338     | 21338               | 0.00                         | 25.54                           |
| 21951     | 21338               | 1.21                         | 25.89                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe

mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Arginine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20391-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Arginine; Argininum

### Special notes

When selecting the *Arginine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Arginine*:

| Supplier | Substance | Batch     | Sample ID | Spectra | Certificate        |
|----------|-----------|-----------|-----------|---------|--------------------|
| Fagron   | Arginine  | 13J28-B02 | 21226     | 40      | AR-15-FG-008045-01 |
| Euro OTC | Arginine  | 1604003   | 22514     | 40      | 20160425*          |
| Euro OTC | Arginine  | 1608031   | 22801     | 40      | 20160916*          |
| Euro OTC | Arginine  | 1702014   | 23154     | 40      | 20170316*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Arginine*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 4 reference samples from the substance/substance group *Arginine*.

| Supplier | Substance | Batch       | Sample ID | Spectra |
|----------|-----------|-------------|-----------|---------|
| Fagron   | Arginine  | L11070165   | 20391     | 40      |
| Fagron   | Arginine  | 10H11-N05   | 20416     | 40      |
| Fagron   | Arginine  | 11H01-N05   | 20435     | 40      |
| Euro OTC | Arginine  | L1405020-01 | 21712     | 60      |

- 146 549 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 35 spectra from 10 *Apo-Ident* customers from 21 batches from the substance/substance group *Arginine*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier        | Substance | Batch            | Spectra |
|-----------------|-----------|------------------|---------|
| Caelo           | Arginine  | 1410018-01       | 1       |
| Fagron          | Arginine  | 14I24-B08-303901 | 1       |
| Fagron          | Arginine  | 14B25-B04        | 2       |
| Euro OTC        | Arginine  | 1604003-01       | 1       |
| Euro OTC        | Arginine  | L1405020-01      | 4       |
| Euro OTC        | Arginine  | L1410018-01      | 2       |
| Euro OTC        | Arginine  | L1503033-01      | 3       |
| Euro OTC        | Arginine  | L1510019-01      | 1       |
| Euro OTC        | Arginine  | L1311033-01      | 2       |
| Euro OTC        | Arginine  | 1105040-01       | 1       |
| Phönix 17.09.12 | Arginine  | 1110017-01       | 1       |
| Fagron          | Arginine  | 13/24-N01        | 1       |
| Fagron          | Arginine  | 13F14-N02        | 2       |
| Fagron          | Arginine  | 13I24-N01        | 1       |
| Euro OTC        | Arginine  | L1209035-01      | 1       |
| Euro OTC        | Arginine  | L1102030-01      | 2       |
| Euro OTC        | Arginine  | L1206006-01      | 2       |
| Euro OTC        | Arginine  | L1302006-01      | 2       |
| Phönix          | Arginine  | L1302006-01      | 1       |
| Fargon          | Arginine  | 121429           | 1       |
| Fagron          | Arginine  | 12C21-N04        | 2       |
| Fagron          | Arginine  | 13J28-B02-290463 | 1       |

- 69 598 spectra from 414 *Apo-Ident* customers from a total of 23 780 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Arginine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Arginine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 180           | 0              | 146 549       |
| <b>Type C</b> | 0              | 35            | 0              | 69 598        |

The substance/substance group *Arginine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.6667 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 82.8571 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21226     | 21226               | 0.00                         | 36.33                           |
| 22514     | 22514               | 0.00                         | 33.65                           |
| 22801     | 22801               | 0.00                         | 34.35                           |
| 23154     | 23154               | 0.00                         | 34.94                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Arginine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20657-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Arginine hydrochloride; Arginini hydrochloridum; Argininum hydrochloricum

### Special notes

When selecting the *Arginine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Arginine hydrochloride*:

| Supplier | Substance           | Batch       | Sample ID | Spectra | Certificate        |
|----------|---------------------|-------------|-----------|---------|--------------------|
| Euro OTC | Arginine hydroch... | L1103042-01 | 20657     | 40      | 20110325           |
| Euro OTC | Arginine hydroch... | L1212009-01 | 20964     | 40      | 1402430            |
| Euro OTC | Arginine hydroch... | 1306023-01  | 21776     | 40      | AR-15-FG-008412-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Arginine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *Arginine hydrochloride*.

| Supplier | Substance              | Batch      | Sample ID          | Spectra |
|----------|------------------------|------------|--------------------|---------|
| Euro OTC | Arginine hydrochloride | 1306023-01 | 21776 <sup>†</sup> | 20      |
| Euro OTC | Arginine hydrochloride | 1603033    | 22512              | 40      |
| Euro OTC | Arginine hydrochloride | 1610042    | 22877              | 40      |

- 146 629 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 18 spectra from 6 *Apo-Ident* customers from 13 batches from the substance/substance group *Arginine hydrochloride*.

| Supplier | Substance              | Batch      | Spectra |
|----------|------------------------|------------|---------|
| Euro OTC | Arginine hydrochloride | 1306023-01 | 1       |
| EuRho    | Arginine hydrochloride | 1306023-01 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

continued from previous page

| Supplier                   | Substance              | Batch            | Spectra |
|----------------------------|------------------------|------------------|---------|
| Fagron                     | Arginine hydrochloride | 13J28-B03        | 2       |
| Fagron                     | Arginine hydrochloride | 13J28-B03-287766 | 1       |
| Hirundo Products Vertri... | Arginine hydrochloride | 6412784-152      | 2       |
| Euro OTC                   | Arginine hydrochloride | L1407040-01      | 1       |
| Euro OTC                   | Arginine hydrochloride | L1407040-02      | 1       |
| Euro OTC                   | Arginine hydrochloride | L1506023-01      | 1       |
| Fagron                     | Arginine hydrochloride | 12C20-N08        | 1       |
| Fagron                     | Arginine hydrochloride | 12G25-N13        | 1       |
| Fagron                     | Arginine hydrochloride | 13J28-B032x      | 1       |
| Fagron                     | Arginine hydrochloride | 13j28-B03-287768 | 1       |
| Fagron                     | Arginine hydrochloride | 13j28-b03-287768 | 1       |
| Euro OTC                   | Arginine hydrochloride | L1212009-01      | 3       |

- 69 615 spectra from 414 *Apo-Ident* customers from a total of 23 788 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Arginine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Arginine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 100           | 0              | 146 629       |
| <b>Type C</b> | 0              | 17            | 1              | 69 615        |

The substance/substance group *Arginine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20657     | 21776               | 11.48                        | 47.90                           |
| 20964     | 20964               | 0.00                         | 48.03                           |
| 21776     | 21776               | 0.00                         | 46.44                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ascorbic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20394-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ascorbic acid; Acidum ascorbicum; Acidum ascorbinicum

### Special notes

When selecting the *Ascorbic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ascorbic acid*:

| Supplier | Substance     | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------|-----------|-----------|---------|-------------|
| Fagron   | Ascorbic acid | 13G29-B07 | 21229     | 40      | 1410500     |
| Caelo    | Ascorbic acid | 12350011  | 21317     | 40      | 20121122    |
| Euro OTC | Ascorbic acid | 1612018   | 22918     | 40      | 20170109*   |
| Caelo    | Ascorbic acid | 163452    | 23062     | 40      | 20170125*   |
| Caelo    | Ascorbic acid | 171358    | 23293     | 40      | 20170524*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Ascorbic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 460 spectra of 11 reference samples from the substance/substance group *Ascorbic acid*.

| Supplier                     | Substance     | Batch      | Sample ID | Spectra |
|------------------------------|---------------|------------|-----------|---------|
| Caelo                        | Ascorbic acid | 9306404    | 20394     | 40      |
| Hebei Welcome Pharmaceu. ... | Ascorbic acid | 1107411106 | 20430     | 40      |
| Caelo                        | Ascorbic acid | 160569     | 22483     | 60      |
| Euro OTC                     | Ascorbic acid | 1607025    | 22672     | 40      |
| Euro OTC                     | Ascorbic acid | 1605024    | 22680     | 40      |
| Euro OTC                     | Ascorbic acid | 1609015    | 22789     | 40      |
| Euro OTC                     | Ascorbic acid | 1703040    | 23128     | 40      |
| Euro OTC                     | Ascorbic acid | 1703025    | 23144     | 40      |
| Caelo                        | Ascorbic acid | 171358     | 23288     | 40      |
| Euro OTC                     | Ascorbic acid | 1707005    | 23553     | 40      |
| Euro OTC                     | Ascorbic acid | 1708026    | 23701     | 40      |

- 146 269 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 56 spectra from 33 *Apo-Ident* customers from 48 batches from the substance/substance group *Ascorbic acid*.

| Supplier                   | Substance     | Batch          | Spectra |
|----------------------------|---------------|----------------|---------|
| Caelo                      | Ascorbic acid | 14123809       | 2       |
| Caelo                      | Ascorbic acid | 15300002       | 2       |
| Caelo                      | Ascorbic acid | 1071404        | 1       |
| Euro OTC                   | Ascorbic acid | 10071418       | 1       |
| Euro OTC                   | Ascorbic acid | 12061408       | 1       |
| Euro OTC                   | Ascorbic acid | 1308008-01     | 1       |
| Caelo                      | Ascorbic acid | 12350011       | 1       |
| pharmorgana                | Ascorbic acid | 1304413505     | 1       |
| Caelo                      | Ascorbic acid | 13341803/3     | 1       |
| Caelo                      | Ascorbic acid | 15084503       | 1       |
| Caelo                      | Ascorbic acid | 14123910       | 1       |
| Caelo                      | Ascorbic acid | 15084507       | 1       |
| Caelo                      | Ascorbic acid | 14123915       | 1       |
| Caelo                      | Ascorbic acid | 14214403       | 1       |
| Euro OTC                   | Ascorbic acid | 17041406       | 1       |
| Euro OTC                   | Ascorbic acid | L-1202011-02   | 1       |
| Pharma Greven              | Ascorbic acid | D201503108     | 1       |
| Gehe/Gehe                  | Ascorbic acid | L1505001       | 1       |
| Nachprüfung                | Ascorbic acid | VC1242         | 2       |
| Canea Pharma/Sanacorp      | Ascorbic acid | VC1450         | 1       |
| Zentiva/Alliance Health... | Ascorbic acid | 15300007       | 1       |
| Caelo                      | Ascorbic acid | 15300007       | 2       |
| Caelo                      | Ascorbic acid | 15359003       | 1       |
| Caelo                      | Ascorbic acid | 2061203        | 1       |
| Euro OTC                   | Ascorbic acid | 11121302       | 1       |
| NCPC                       | Ascorbic acid | 1107411106     | 1       |
| Caelo                      | Ascorbic acid | 11208606       | 1       |
| Caesar & Loretz GmbH       | Ascorbic acid | 11208606       | 1       |
| Caelo                      | Ascorbic acid | 11208608       | 1       |
| REWE Food Ingredients      | Ascorbic acid | 11572008237103 | 1       |
| Fagron                     | Ascorbic acid | 12/25-N04      | 1       |
| Caelo                      | Ascorbic acid | 12272601/1     | 1       |
| Caelo                      | Ascorbic acid | 12349909       | 1       |
| Caelo                      | Ascorbic acid | 12350003       | 1       |
| Caelo                      | Ascorbic acid | 12350005       | 2       |
| Euro OTC                   | Ascorbic acid | 28081303       | 1       |
| Premium Ingredients Int... | Ascorbic acid | 2012444403     | 1       |
| NE GPF                     | Ascorbic acid | DY0261121205   | 1       |
| Gesundform                 | Ascorbic acid | L1110704       | 1       |
| Amos Vital                 | Ascorbic acid | L1120454       | 1       |
| AmsVital GmbH              | Ascorbic acid | L1220572       | 1       |
| Euro OTC                   | Ascorbic acid | L1202011-02    | 1       |
| Wepa Paulus                | Ascorbic acid | 11406201       | 1       |
| Caelo                      | Ascorbic acid | 14214404       | 1       |
| Caelo                      | Ascorbic acid | 14044701/3     | 1       |
| Euro OTC                   | Ascorbic acid | 17011404       | 1       |
| Caelo                      | Ascorbic acid | 22101302       | 1       |
| Wepa                       | Ascorbic acid | 261120415      | 1       |
| Amos Vital                 | Ascorbic acid | L1230216       | 2       |
| Anzag/Gehe Balance         | Ascorbic acid | L1210232       | 1       |

- 69 577 spectra from 414 *Apo-Ident* customers from a total of 23 753 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ascorbic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ascorbic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 200           | 0              | 71 186        |
| Type B | 0              | 460           | 0              | 146 269       |
| Type C | 0              | 54            | 2              | 69 577        |

The substance/substance group *Ascorbic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.6957 %) |
| Type C | 100.0000 % (> 99.8813 %) | 96.4286 % (> 91.0714 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21229     | 21229               | 0.00                         | 61.04                           |
| 21317     | 21229               | 3.16                         | 61.12                           |
| 22918     | 22918               | 0.00                         | 62.12                           |
| 23062     | 23062               | 0.00                         | 60.79                           |
| 23293     | 23293               | 0.00                         | 59.95                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe

mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ascorbyl palmitate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21053-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ascorbyl palmitate; Acidum palmitoylascorbicicum; Ascorbylis palmitas

### Special notes

When selecting the *Ascorbyl palmitate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ascorbyl palmitate*:

| Supplier | Substance          | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------------|------------------|-----------|---------|-------------|
| Fagron   | Ascorbyl palmitate | 13K04-N01        | 21053     | 40      | 1403226     |
| Fagron   | Ascorbyl palmitate | 13C06-B40-291206 | 21665     | 40      | 20140306    |
| Fagron   | Ascorbyl palmitate | 15F01-B99-309774 | 21851     | 40      | 20150615    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Ascorbyl palmitate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 3 reference samples from the substance/substance group *Ascorbyl palmitate*.

| Supplier | Substance          | Batch            | Sample ID          | Spectra |
|----------|--------------------|------------------|--------------------|---------|
| Fagron   | Ascorbyl palmitate | 13C06-B40-291206 | 21665 <sup>†</sup> | 20      |
| Fagron   | Ascorbyl palmitate | 15F01-B99-309774 | 21851 <sup>†</sup> | 20      |
| Fagron   | Ascorbyl palmitate | 17E18-B06-335527 | 23520              | 40      |

- 146 649 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 36 spectra from 17 *Apo-Ident* customers from 22 batches from the substance/substance group *Ascorbyl palmitate*.

| Supplier | Substance          | Batch            | Spectra |
|----------|--------------------|------------------|---------|
| Fagron   | Ascorbyl palmitate | 15f01-b99-309774 | 1       |
| Fagron   | Ascorbyl palmitate | 16I30-B03-330625 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



continued from previous page

| Supplier                   | Substance          | Batch            | Spectra |
|----------------------------|--------------------|------------------|---------|
| Bionorica                  | Ascorbyl palmitate | 74962            | 1       |
| Bionorica EthicsGmbH/Sa... | Ascorbyl palmitate | 74736            | 1       |
| Bionorica                  | Ascorbyl palmitate | 74736            | 1       |
| Bionorica/Noweda           | Ascorbyl palmitate | 77773            | 2       |
| Bionorica Ethics7Noweda    | Ascorbyl palmitate | 82275            | 2       |
| Bionorica Ethics/ Noweda   | Ascorbyl palmitate | 85532            | 2       |
| Bionorica ethics           | Ascorbyl palmitate | 85532            | 2       |
| Fagron                     | Ascorbyl palmitate | 13C06-B40-291206 | 2       |
| Fagron                     | Ascorbyl palmitate | 14I03-N01        | 1       |
| Fagron                     | Ascorbyl palmitate | 15F01-B99        | 1       |
| Fagron                     | Ascorbyl palmitate | 15F01-B99-525121 | 3       |
| Caelo                      | Ascorbyl palmitate | 15F01-B99-525121 | 1       |
| Fagron                     | Ascorbyl palmitate | 15F01-B99-525122 | 1       |
| Fagron                     | Ascorbyl palmitate | 16/30-B03-329375 | 1       |
| Caelo                      | Ascorbyl palmitate | 16810-B04525199  | 1       |
| Fagron                     | Ascorbyl palmitate | 16B10-B04-525199 | 1       |
| Caelo                      | Ascorbyl palmitate | 16B10-B04324111  | 1       |
| Fagron                     | Ascorbyl palmitate | 16I30-B03-326543 | 1       |
| Fagron                     | Ascorbyl palmitate | 16I30-B03-329375 | 1       |
| Fagron                     | Ascorbyl palmitate | 16I30-B03-525358 | 2       |
| Fagron                     | Ascorbyl palmitate | 16I30-B03-525380 | 2       |
| Fagron                     | Ascorbyl palmitate | 17E18-B06        | 1       |
| Bionorica                  | Ascorbyl palmitate | 82275            | 1       |
| PHOENIX 30.06.2014         | Ascorbyl palmitate | UQ21206229       | 1       |
| Bionorica                  | Ascorbyl palmitate | 85532            | 1       |

- 69 597 spectra from 414 *Apo-Ident* customers from a total of 23 779 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ascorbyl palmitate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ascorbyl palmitate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 29            | 7              | 69 597        |

The substance/substance group *Ascorbyl palmitate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 80.5556 % (> 72.2222 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21053     | 21053               | 0.00                         | 59.23                           |
| 21665     | 21053               | 13.12                        | 52.70                           |
| 21851     | 21053               | 14.70                        | 52.35                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Atropine sulfate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20653-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Atropine sulfate; Atropine sulphate; Atropini sulfas; Atropinum sulfuricum

### Special notes

When selecting the *Atropine sulfate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Atropine sulfate*:

| Supplier | Substance        | Batch    | Sample ID | Spectra | Certificate |
|----------|------------------|----------|-----------|---------|-------------|
| Caelo    | Atropine sulfate | 11180602 | 20653     | 40      | 1405538     |
| Caelo    | Atropine sulfate | 13173808 | 21088     | 40      | 1403483     |
| Caelo    | Atropine sulfate | 13357405 | 21551     | 45      | 1504594     |
| Caelo    | Atropine sulfate | 14336806 | 21719     | 40      | 1510209     |
| Caelo    | Atropine sulfate | 15301601 | 21920     | 40      | 20150930    |
| Caelo    | Atropine sulfate | 14336806 | 21719SI   | 40      | 1510209     |
| Caelo    | Atropine sulfate | 15301601 | 21920SI   | 40      | 20150930    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 285 spectra of 7 reference samples from the substance/substance group *Atropine sulfate*. These samples are listed above in the [calibration samples](#) section.
- 71 101 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 390 spectra of 12 reference samples from the substance/substance group *Atropine sulfate*.

| Supplier | Substance        | Batch            | Sample ID            | Spectra |
|----------|------------------|------------------|----------------------|---------|
| Caelo    | Atropine sulfate | 14336806         | 21719 <sup>†</sup>   | 20      |
| Caelo    | Atropine sulfate | 15301601         | 21920 <sup>†</sup>   | 20      |
| Fagron   | Atropine sulfate | 16G20-B06-328437 | 22932                | 40      |
| Caelo    | Atropine sulfate | 16326802         | 22952                | 40      |
| Caelo    | Atropine sulfate | 170264           | 23367                | 40      |
| Caelo    | Atropine sulfate | 172732           | 23682                | 40      |
| Caelo    | Atropine sulfate | 14336806         | 21719SI <sup>†</sup> | 20      |
| Caelo    | Atropine sulfate | 15301601         | 21920SI <sup>†</sup> | 20      |
| Fagron   | Atropine sulfate | 16G20-B06-328437 | 22932SI              | 40      |
| Caelo    | Atropine sulfate | 16326802         | 22952SI              | 40      |
| Caelo    | Atropine sulfate | 170264           | 23367SI              | 40      |
| Caelo    | Atropine sulfate | 172732           | 23682SI              | 30      |

- 146 339 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 12 spectra from 9 *Apo-Ident* customers from 10 batches from the substance/substance group *Atropine sulfate*.

| Supplier | Substance        | Batch     | Spectra |
|----------|------------------|-----------|---------|
| Caelo    | Atropine sulfate | 13357403  | 1       |
| Caelo    | Atropine sulfate | 13357405  | 1       |
| Caelo    | Atropine sulfate | 14336807  | 1       |
| Caelo    | Atropine sulfate | 15115201  | 3       |
| Phönix   | Atropine sulfate | 15301607  | 1       |
| Gehe     | Atropine sulfate | 16326802  | 1       |
| Caelo    | Atropine sulfate | 12244206  | 1       |
| Noweda   | Atropine sulfate | 12250403  | 1       |
| Caelo    | Atropine sulfate | 13173809  | 1       |
| fargon   | Atropine sulfate | 13K01-N01 | 1       |

- 69 621 spectra from 414 *Apo-Ident* customers from a total of 23 791 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Atropine sulfate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Atropine sulfate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 285           | 0              | 71 101        |
| <b>Type B</b> | 0              | 390           | 0              | 146 339       |
| <b>Type C</b> | 0              | 12            | 0              | 69 621        |

The substance/substance group *Atropine sulfate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.8947 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.4615 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20653     | 20653               | 0.00                         | 31.28                           |
| 21088     | 21088               | 0.00                         | 31.28                           |
| 21551     | 21551               | 0.00                         | 29.86                           |
| 21719     | 21719               | 0.00                         | 30.28                           |
| 21920     | 21719               | 12.51                        | 30.50                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Bacitracin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20851-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Bacitracin; Bacitracinum

### Special notes

When selecting the *Bacitracin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Bacitracin*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate |
|----------|------------|------------------|-----------|---------|-------------|
| Fagron   | Bacitracin | 13A-03-N11       | 20851     | 20      | 1401189     |
| Fagron   | Bacitracin | 14A21-B09-292909 | 21657     | 40      | 1511741     |
| Roth     | Bacitracin | 194169081        | 21658     | 40      | 20140508    |
| Fagron   | Bacitracin | 14E23-B03-296243 | 21686     | 30      | 1503715     |
| Fagron   | Bacitracin | 15C12-B06-309185 | 21898     | 40      | 20150324    |
| Fagron   | Bacitracin | 15C12-B06-309185 | 21986     | 40      | 9466        |
| Fagron   | Bacitracin | 16B17-B03-322939 | 22739     | 40      | 20160421    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 250 spectra of 7 reference samples from the substance/substance group *Bacitracin*. These samples are listed above in the [calibration samples](#) section.
- 71 136 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 320 spectra of 10 reference samples from the substance/substance group *Bacitracin*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Fagron   | Bacitracin | 9J30-N01         | 20218              | 40      |
| Fagron   | Bacitracin | 13A-03-N11       | 20851 <sup>†</sup> | 20      |
| Fagron   | Bacitracin | 14A21-B09-292909 | 21657 <sup>†</sup> | 20      |
| Roth     | Bacitracin | 194169081        | 21658 <sup>†</sup> | 20      |
| Fagron   | Bacitracin | 14E23-B03-296243 | 21686 <sup>†</sup> | 30      |
| Fagron   | Bacitracin | 15C12-B06-309185 | 21898 <sup>†</sup> | 20      |
| Fagron   | Bacitracin | 15C12-B06-309185 | 21986 <sup>†</sup> | 20      |
| Fagron   | Bacitracin | 16I12-B03-334194 | 23531              | 30      |
| Fagron   | Bacitracin | 14A21-B09-292909 | 21657SI            | 60      |
| Fagron   | Bacitracin | 15C12-B06-309185 | 21898SI            | 60      |

- 146 409 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 59 spectra from 36 *Apo-Ident* customers from 35 batches from the substance/substance group *Bacitracin*.

| Supplier      | Substance  | Batch            | Spectra |
|---------------|------------|------------------|---------|
| Fagron        | Bacitracin | 11E23-N10        | 1       |
| Fagron        | Bacitracin | 11J17-N01        | 2       |
| Fagron        | Bacitracin | 11/17-N01        | 1       |
| Fagron        | Bacitracin | 12G12-N17        | 1       |
| Fagron        | Bacitracin | 13A03-N11        | 1       |
| Fagron        | Bacitracin | 13B25-B01        | 1       |
| Fagron        | Bacitracin | 13D26-N08        | 1       |
| Fagron        | Bacitracin | 14A21-B09        | 2       |
| Fagron        | Bacitracin | 14A21-B09-290643 | 2       |
| Fagron        | Bacitracin | 14A21-B09-290645 | 2       |
| Fagron        | Bacitracin | 14A21-B09-292908 | 2       |
| Caelo         | Bacitracin | 14A21-B09-292908 | 1       |
| Fagron        | Bacitracin | 14E23-B03        | 3       |
| Fagron        | Bacitracin | 14E23-B03-296243 | 6       |
| Fagron        | Bacitracin | 14e23-b03-296243 | 1       |
| Fagron        | Bacitracin | 14E23-B03-296245 | 2       |
| Fagraon       | Bacitracin | 14E23-B03-303424 | 1       |
| Caelo         | Bacitracin | 14E23-B03-296243 | 2       |
| Fagron        | Bacitracin | 14E23B03-303424  | 1       |
| Fagron        | Bacitracin | 14E23-B03-303424 | 1       |
| Fagron        | Bacitracin | 14E23-B03-303425 | 1       |
| Fagron        | Bacitracin | 14E23-B03-333424 | 1       |
| Caelo         | Bacitracin | 15080605         | 1       |
| Fagron        | Bacitracin | 15C12-B06        | 1       |
| Fagron        | Bacitracin | 15C12-B06-309185 | 1       |
| Fargon/Phönix | Bacitracin | 15C12-B06-312975 | 1       |
| Caelo         | Bacitracin | 15C12-B06-317782 | 1       |
| Fagron        | Bacitracin | 16B17-B03        | 2       |
| Fagron        | Bacitracin | 16B17-B03-322891 | 4       |
| Caelo         | Bacitracin | 16B17-B03-322891 | 1       |
| Fagron        | Bacitracin | 16b17-b03-322939 | 1       |
| Fagron        | Bacitracin | 211531           | 1       |
| Fagron        | Bacitracin | 28051509         | 1       |
| Fagron        | Bacitracin | 31071503         | 1       |
| Fagron        | Bacitracin | C2280017         | 3       |
| Phönix Gotha  | Bacitracin | C2280010         | 1       |
| Fagron        | Bacitracin | 700193-0001      | 1       |
| Fagron        | Bacitracin | C2280065         | 1       |
| Fagron        | Bacitracin | 13C13-N10        | 1       |

- 69 574 spectra from 414 *Apo-Ident* customers from a total of 23 766 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Bacitracin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Bacitracin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table

breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 250           | 0              | 71 136        |
| Type B | 0              | 265           | 55             | 146 409       |
| Type C | 0              | 53            | 6              | 69 574        |

The substance/substance group *Bacitracin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.6000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 82.8125 % (> 81.8750 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 89.8305 % (> 84.7458 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20851     | 20851               | 0.00                         | 24.10                           |
| 21657     | 21657               | 0.00                         | 24.65                           |
| 21658     | 21986               | 3.92                         | 26.17                           |
| 21686     | 21686               | 0.00                         | 24.87                           |
| 21898     | 21986               | 4.26                         | 25.48                           |
| 21986     | 21986               | 0.00                         | 24.68                           |
| 22739     | 21986               | 8.06                         | 25.49                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Beclometasone dipropionate, anhydrous</b>                    |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 21046-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Beclometasone dipropionate, anhydrous; Beclometasoni dipropionas anhydricus; Beclometasonum dipropionicum anhydricum

### Special notes

When selecting the *Beclometasone dipropionate, anhydrous* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Beclometasone dipropionate, anhydrous*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Beclometasone di... | 13I05-N03        | 21046     | 40      | 1511689     |
| Fagron   | Beclometasone di... | 13E02B40293328   | 21554     | 40      | 20140508    |
| Euro OTC | Beclometasone di... | 1203022-03       | 21634     | 25      | 1509281     |
| Fagron   | Beclometasone di... | 13E02-B40-296353 | 21977     | 40      | 20140508    |

*continued on the next page*

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Beclometasone di... | 1502032          | 22989     | 40      | 20150327*   |
| Fagron   | Beclometasone di... | 13E02-B40-296353 | 21977SI   | 20      | 20140508    |
| Euro OTC | Beclometasone di... | 1502032          | 22989SI   | 30      | 20150327*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 235 spectra of 7 reference samples from the substance/substance group *Beclometasone dipropionate, anhydrous*. These samples are listed above in the [calibration samples](#) section.
- 71151 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 252 spectra of 8 reference samples from the substance/substance group *Beclometasone dipropionate, anhydrous*.

| Supplier | Substance                       | Batch            | Sample ID            | Spectra |
|----------|---------------------------------|------------------|----------------------|---------|
| Fagron   | Beclometasone dipropionate, ... | 11C01-N03        | 20293                | 40      |
| Euro OTC | Beclometasone dipropionate, ... | 1203022-03       | 21634 <sup>†</sup>   | 35      |
| Fagron   | Beclometasone dipropionate, ... | 13E02-B40-296353 | 21977 <sup>†</sup>   | 20      |
| Euro OTC | Beclometasone dipropionate, ... | 1203022-03       | 21995                | 60      |
| Fagron   | Beclometasone dipropionate, ... | 15F29-B09-314376 | 23104                | 40      |
| Fagron   | Beclometasone dipropionate, ... | 13E02-B40-296353 | 21977SI <sup>†</sup> | 9       |
| Euro OTC | Beclometasone dipropionate, ... | 1203022-03       | 21995SI              | 28      |
| Fagron   | Beclometasone dipropionate, ... | 15F29-B09-314376 | 23104SI              | 20      |

- 146477 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 39 spectra from 10 *Apo-Ident* customers from 23 batches from the substance/substance group *Beclometasone dipropionate, anhydrous*.

| Supplier | Substance                       | Batch            | Spectra |
|----------|---------------------------------|------------------|---------|
| Fagron   | Beclometasone dipropionate, ... | 13E02-B40        | 1       |
| Euro OTC | Beclometasone dipropionate, ... | 1203022-03       | 1       |
| Fagron   | Beclometasone dipropionate, ... | 13/05-N03        | 1       |
| Fagron   | Beclometasone dipropionate, ... | 13/05-N03        | 1       |
| Fagron   | Beclometasone dipropionate, ... | 13E02-B40-293327 | 4       |
| Fagron   | Beclometasone dipropionate, ... | 13E02-B40-293328 | 2       |
| Fagron   | Beclometasone dipropionate, ... | 13E02-B40-296353 | 1       |
| Fagron   | Beclometasone dipropionate, ... | 13E02-B40-296354 | 2       |
| Fagron   | Beclometasone dipropionate, ... | 13I05-N03        | 3       |
| Fagron   | Beclometasone dipropionate, ... | 13I05N03         | 1       |
| Fagron   | Beclometasone dipropionate, ... | 14D04-B04-302335 | 1       |
| Fagron   | Beclometasone dipropionate, ... | 14D04-B04-302336 | 3       |
| Fagron   | Beclometasone dipropionate, ... | 14D04-B04302336  | 1       |
| Fagron   | Beclometasone dipropionate, ... | 16B16-B03-322517 | 1       |
| fragon   | Beclometasone dipropionate, ... | 700721-0004      | 1       |
| Fagron   | Beclometasone dipropionate, ... | C0783/112020     | 1       |
| Fagron   | Beclometasone dipropionate, ... | 11F28-N02        | 2       |
| Euro OTC | Beclometasone dipropionate, ... | C0783111020      | 1       |
| Euro OTC | Beclometasone dipropionate, ... | 1203022-01       | 1       |
| Fagron   | Beclometasone dipropionate, ... | 12D12-N03        | 5       |
| Fagron   | Beclometasone dipropionate, ... | 12G04-N11        | 3       |
| Caelo    | Beclometasone dipropionate, ... | 12G04-n11        | 1       |
| Caelo    | Beclometasone dipropionate, ... | 13E02-B40-293326 | 1       |

- 69 594 spectra from 414 *Apo-Ident* customers from a total of 23 778 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Beclometasone dipropionate, anhydrous* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Beclometasone dipropionate, anhydrous* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 235           | 0              | 71 151        |
| <b>Type B</b> | 0              | 252           | 0              | 146 477       |
| <b>Type C</b> | 0              | 37            | 2              | 69 594        |

The substance/substance group *Beclometasone dipropionate, anhydrous* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.4468 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.6190 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 94.8718 % (> 87.1795 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21046            | 21046                      | 0.00                                | 37.86                                  |
| 21554            | 21634                      | 4.32                                | 36.97                                  |
| 21634            | 21634                      | 0.00                                | 39.00                                  |
| 21977            | 22989                      | 3.60                                | 33.75                                  |
| 22989            | 22989                      | 0.00                                | 36.86                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Benzocaine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20211-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Benzocaine; Aethylium paraaminobenzoicum; Benzocainum

### Special notes

When selecting the *Benzocaine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Benzocaine*:

| Supplier | Substance  | Batch     | Sample ID | Spectra | Certificate |
|----------|------------|-----------|-----------|---------|-------------|
| Caelo    | Benzocaine | 12341904  | 20843     | 40      | 1411055     |
| Fagron   | Benzocaine | 12E04-N06 | 21083     | 40      | 20120607    |
| Caelo    | Benzocaine | 13213509  | 21563     | 40      | 1706017     |



## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Benzocaine*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 6 reference samples from the substance/substance group *Benzocaine*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Fagron   | Benzocaine | 10K02-N01        | 20211              | 40      |
| Fagron   | Benzocaine | 10K02-N01        | 20219              | 40      |
| Caelo    | Benzocaine | 13213509         | 21563 <sup>†</sup> | 20      |
| Caelo    | Benzocaine | 161740           | 22641              | 40      |
| Fagron   | Benzocaine | 14G02-B01-306980 | 23569              | 40      |
| Caelo    | Benzocaine | 172174           | 23628              | 40      |

- 146 509 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 141 spectra from 93 *Apo-Ident* customers from 68 batches from the substance/substance group *Benzocaine*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier       | Substance  | Batch            | Spectra |
|----------------|------------|------------------|---------|
| Fagron         | Benzocaine | 11K08-B40        | 4       |
| Caelo          | Benzocaine | 13213502         | 5       |
| Caelo          | Benzocaine | 13213511         | 3       |
| Caelo          | Benzocaine | 2412M-01118      | 1       |
| Fagron         | Benzocaine | 12H10-N06        | 4       |
| Caelo          | Benzocaine | 12341904         | 6       |
| Fagron         | Benzocaine | 400313           | 1       |
| Caelo          | Benzocaine | 5021401          | 1       |
| Caelo          | Benzocaine | 10072603         | 1       |
| Caelo          | Benzocaine | 6031501          | 1       |
| Caelo          | Benzocaine | 1012ben          | 1       |
| Fagron         | Benzocaine | 104210-0001      | 1       |
| Fagron         | Benzocaine | 10K02-N01        | 1       |
| Fagron         | Benzocaine | 11/22-N03        | 1       |
| Fagron         | Benzocaine | 11/22-N3         | 1       |
| Caelo          | Benzocaine | 11127506         | 1       |
| Caelo          | Benzocaine | 11127508         | 2       |
| Caelo          | Benzocaine | 11305206         | 1       |
| Fagron         | Benzocaine | 11I22-N03        | 1       |
| Fargon/Sana    | Benzocaine | 11K08-290049     | 1       |
| Fagron         | Benzocaine | 11K08B40290050   | 1       |
| Fagron         | Benzocaine | 11K08-B40-291840 | 1       |
| Fagron         | Benzocaine | 11k08-B40-291841 | 1       |
| Fagron         | Benzocaine | 11K08-B40-291841 | 4       |
| Fagron         | Benzocaine | 11k08-b40-291841 | 1       |
| Caelo          | Benzocaine | 12115007         | 5       |
| Caelo          | Benzocaine | 12115008         | 3       |
| Caelo          | Benzocaine | 12115011         | 2       |
| Phönix Gotha   | Benzocaine | 12115011         | 1       |
| Fagron         | Benzocaine | 12E04-N06        | 10      |
| Caelo          | Benzocaine | 12341906         | 1       |
| Fagron         | Benzocaine | 12341904         | 1       |
| Phoenix        | Benzocaine | 12H10-N06        | 1       |
| Fargon         | Benzocaine | 12H10-N06        | 1       |
| Caelo          | Benzocaine | 1313509          | 1       |
| Sanacorp       | Benzocaine | 13213502         | 1       |
| Sanacorp       | Benzocaine | 13213506         | 1       |
| Caelo          | Benzocaine | 13213509         | 6       |
| Anzag / Noweda | Benzocaine | 1321351          | 1       |
| Caelo          | Benzocaine | 13213515         | 2       |
| Caelo          | Benzocaine | 13213516         | 1       |
| Phönix         | Benzocaine | 13F06-N10        | 1       |
| Fagron         | Benzocaine | 13F06-N10        | 1       |
| Fagron         | Benzocaine | 13L06-B02        | 2       |
| Fargron        | Benzocaine | 13L06-B02-294112 | 1       |
| Caelo          | Benzocaine | 13L06-B02-294112 | 1       |
| Fagron         | Benzocaine | 13L06-B02-294100 | 2       |
| Euro OTC       | Benzocaine | 13L06-B02-297505 | 1       |
| Fagron         | Benzocaine | 13L06-B02-300494 | 2       |
| Caelo          | Benzocaine | 14277502         | 3       |
| Fagron         | Benzocaine | 13L06-B06-300481 | 1       |
| Fagron         | Benzocaine | 14G02-B01-310324 | 4       |
| Caelo          | Benzocaine | 1515I-01118      | 1       |
| Caelo          | Benzocaine | 15227302         | 4       |
| Fagron         | Benzocaine | 15227307         | 1       |
| Caelo          | Benzocaine | 15227307         | 3       |
| Caelo          | Benzocaine | 15227311         | 1       |
| Caelo          | Benzocaine | 15227314         | 3       |
| Caelo          | Benzocaine | 15227315         | 3       |
| Fagron         | Benzocaine | 15C19-B04-308254 | 1       |

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| Supplier        | Substance  | Batch            | Spectra |
|-----------------|------------|------------------|---------|
| Fagron          | Benzocaine | 15C19-B04-316239 | 1       |
| Fagron          | Benzocaine | 15C19-B04-322019 | 4       |
| AHD             | Benzocaine | 16174001         | 1       |
| Caelo           | Benzocaine | 16174001         | 2       |
| Caelo           | Benzocaine | 16174007         | 1       |
| Caelo           | Benzocaine | 19031301         | 1       |
| Caelo           | Benzocaine | 24081212         | 1       |
| Caelo           | Benzocaine | 3784947          | 1       |
| Fagron          | Benzocaine | 4413E-01118      | 1       |
| Caelo           | Benzocaine | 91062169         | 1       |
| Fagron          | Benzocaine | BZ-08/11-12      | 1       |
| s.Prüfprotokoll | Benzocaine |                  | 1       |
| Fagron          | Benzocaine | BZ-27/1112       | 1       |
| Caelo           | Benzocaine |                  | 1       |
| Fagron          | Benzocaine | 13L06-B02297505  | 1       |
| Fagron          | Benzocaine | 14G02B01318318   | 1       |
| Fagron          | Benzocaine | 15C19-B04        | 1       |

- 69 492 spectra from 414 *Apo-Ident* customers from a total of 23 735 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Benzocaine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Benzocaine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 215           | 5              | 146 509       |
| <b>Type C</b> | 0              | 137           | 4              | 69 492        |

The substance/substance group *Benzocaine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 97.7273 % (> 96.3636 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 97.1631 % (> 95.0355 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20843     | 20843               | 0.00                         | 96.05                           |
| 21083     | 21563               | 35.40                        | 87.56                           |
| 21563     | 21563               | 0.00                         | 96.60                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Benzoic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20041-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Benzoic acid; Acidum benzoicum

### Special notes

When selecting the *Benzoic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Benzoic acid*:

| Supplier | Substance    | Batch    | Sample ID | Spectra | Certificate |
|----------|--------------|----------|-----------|---------|-------------|
| Caelo    | Benzoic acid | 13391310 | 21458     | 40      | 20131216    |
| Caelo    | Benzoic acid | 15084611 | 23095     | 40      | 20150318    |
| Caelo    | Benzoic acid | 15084614 | 23096     | 40      | 1707644     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Benzoic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 93 spectra of 3 reference samples from the substance/substance group *Benzoic acid*.

| Supplier | Substance    | Batch    | Sample ID          | Spectra |
|----------|--------------|----------|--------------------|---------|
| Fagron   | Benzoic acid | 9B25-N03 | 20041              | 33      |
| Caelo    | Benzoic acid | 13391310 | 21458 <sup>†</sup> | 20      |
| Caelo    | Benzoic acid | 15084614 | 22664              | 40      |

- 146 636 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 22 spectra from 17 *Apo-Ident* customers from 12 batches from the substance/substance group *Benzoic acid*.

| Supplier | Substance    | Batch    | Spectra |
|----------|--------------|----------|---------|
| Caelo    | Benzoic acid | 1339120  | 1       |
| Caelo    | Benzoic acid | 13391310 | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier              | Substance    | Batch         | Spectra |
|-----------------------|--------------|---------------|---------|
| Caelo                 | Benzoic acid | 15084603      | 2       |
| Caelo                 | Benzoic acid | 15084607      | 3       |
| Caelo                 | Benzoic acid | 13391320      | 1       |
| Caleo/Phoenix         | Benzoic acid | 15084607      | 1       |
| Sanacorp              | Benzoic acid | 15084607      | 1       |
| Caelo                 | Benzoic acid | 15084701      | 1       |
| Gatt-Koller / Phoenix | Benzoic acid | 2992/07131314 | 2       |
| Caelo                 | Benzoic acid | 10156104      | 1       |
| Phönix                | Benzoic acid | 13074605      | 1       |
| Caelo                 | Benzoic acid | 13074605      | 3       |
| Caelo                 | Benzoic acid | 13074610      | 2       |
| Caelo                 | Benzoic acid | 90179109      | 1       |
| Caelo                 | Benzoic acid | 13391314      | 1       |

- 69 611 spectra from 414 *Apo-Ident* customers from a total of 23 789 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Benzoic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Benzoic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 72            | 21             | 146 636       |
| <b>Type C</b> | 0              | 19            | 3              | 69 611        |

The substance/substance group *Benzoic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 77.4194 % (> 74.1935 %)  |
| <b>Type C</b> | 100.0000 % (> 99.9813 %) | 86.3636 % (> 72.7273 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21458     | 23096               | 10.56                        | 52.59                           |
| 23095     | 23096               | 10.20                        | 53.70                           |
| 23096     | 23096               | 0.00                         | 58.60                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Benzydamine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20624-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Benzydamine hydrochloride; Benzydamini hydrochloridum; Benzydaminum hydrochloricum

### Special notes

When selecting the *Benzydamine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Benzydamine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Benzydamine hydr... | 14I30-B04-300713 | 21699     | 30      | AR-15-FG-015977-01 |
| Fagron   | Benzydamine hydr... | 15I17-B02-315060 | 22268     | 40      | 20151211           |
| Fagron   | Benzydamine hydr... | 16D05-B50-332333 | 23203     | 40      | 20170323           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 110 spectra of 3 reference samples from the substance/substance group *Benzydamine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 276 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 115 spectra of 4 reference samples from the substance/substance group *Benzydamine hydrochloride*.

| Supplier | Substance                 | Batch            | Sample ID          | Spectra |
|----------|---------------------------|------------------|--------------------|---------|
| Fagron   | Benzydamine hydrochloride | 12D26-N14        | 20624              | 40      |
| Fagron   | Benzydamine hydrochloride | 14I30-B04-300713 | 21699 <sup>†</sup> | 15      |
| Fagron   | Benzydamine hydrochloride | 15I17-B02-315060 | 22268 <sup>†</sup> | 20      |
| Fagron   | Benzydamine hydrochloride | 16D05-B50-332333 | 23204              | 40      |

- 146 614 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 15 spectra from 12 *Apo-Ident* customers from 14 batches from the substance/substance group *Benzydamine hydrochloride*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance                 | Batch            | Spectra |
|----------|---------------------------|------------------|---------|
| Fagron   | Benzydamine hydrochloride | 12C20-N02        | 1       |
| Fagron   | Benzydamine hydrochloride | 14B25-B01-294054 | 1       |
| Fagron   | Benzydamine hydrochloride | 1503309P         | 1       |
| Fagron   | Benzydamine hydrochloride | 1503313P         | 1       |
| Fagron   | Benzydamine hydrochloride | 15A14-B05        | 1       |
| Fagron   | Benzydamine hydrochloride | 15A14-B05-303068 | 1       |
| Fagron   | Benzydamine hydrochloride | 15I17-B02        | 1       |
| Fagron   | Benzydamine hydrochloride | 16B09-B05-318272 | 2       |
| Fagron   | Benzydamine hydrochloride | 16D05-B50        | 1       |
| Fagron   | Benzydamine hydrochloride | 13H19N06         | 1       |
| Fagron   | Benzydamine hydrochloride | 12j10-n03        | 1       |
| Fagron   | Benzydamine hydrochloride | 13A15-N03        | 1       |
| FARGON   | Benzydamine hydrochloride | 13h19-n06        | 1       |
| Fagron   | Benzydamine hydrochloride | 12K07-N16        | 1       |

- 69 618 spectra from 414 *Apo-Ident* customers from a total of 23 787 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Benzydamine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Benzydamine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 110           | 0              | 71 276        |
| <b>Type B</b> | 0              | 115           | 0              | 146 614       |
| <b>Type C</b> | 0              | 15            | 0              | 69 618        |

The substance/substance group *Benzydamine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.5455 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.7826 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21699     | 21699               | 0.00                         | 35.03                           |
| 22268     | 21699               | 5.43                         | 32.48                           |
| 23203     | 21699               | 7.70                         | 34.03                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Betaine monohydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20498-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Betaine monohydrate; Betainum monohydricum

### Special notes

When selecting the *Betaine monohydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Betaine monohydrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Caelo    | Betaine monohydr... | 12336602         | 20991     | 40      | 1403327     |
| Fagron   | Betaine monohydr... | 14I26-B06-309878 | 21956     | 40      | 20141212    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Betaine monohydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Betaine monohydrate*.

| Supplier | Substance           | Batch            | Sample ID          | Spectra |
|----------|---------------------|------------------|--------------------|---------|
| Caelo    | Betaine monohydrate | 11117715         | 20498              | 40      |
| Fagron   | Betaine monohydrate | 14I26-B06-309878 | 21956 <sup>†</sup> | 20      |
| Fagron   | Betaine monohydrate | 16H03-B04-330370 | 23092              | 40      |
| Fagron   | Betaine monohydrate | 16H03-B04-330370 | 23378              | 40      |

- 146 589 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 2 spectra from 1 *Apo-Ident* customers from 2 batches from the substance/substance group *Betaine monohydrate*.

| Supplier | Substance           | Batch            | Spectra |
|----------|---------------------|------------------|---------|
| Caelo    | Betaine monohydrate | 14A14-B02-292983 | 1       |
| Caelo    | Betaine monohydrate | 4312172831       | 1       |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Betaine monohydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Betaine monohydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 140           | 0              | 146 589       |
| <b>Type C</b> | 0              | 2             | 0              | 69 631        |

The substance/substance group *Betaine monohydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.7143 %) |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20991     | 20991               | 0.00                         | 46.84                           |
| 21956     | 20991               | 2.77                         | 47.50                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Labor-

prüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Betamethasone dipropionate, micronized**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20930-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Betamethasone dipropionate, micronized; Betamethasoni dipropionas micronisatum; Betamethasonum dipropionicum micronisatum

### Special notes

When selecting the *Betamethasone dipropionate, micronized* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Betamethasone dipropionate, micronized*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------|-----------|---------|--------------------|
| Fagron   | Betamethasone di... | 13I17-N05  | 20930     | 40      | 1401377            |
| Caelo    | Betamethasone di... | 13372501   | 21250     | 40      | AR-15-FG-005428-01 |
| Caelo    | Betamethasone di... | 13236803   | 21366     | 40      | 20130730           |
| Euro OTC | Betamethasone di... | 1311023-01 | 21716     | 40      | 1505455            |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Euro OTC | Betamethasone di... | 1601034          | 22372     | 30      | 20160204*          |
| Fagron   | Betamethasone di... | 16C04-B03-324513 | 22898     | 40      | 20160421           |
| Caelo    | Betamethasone di... | 13372501         | 21250SI   | 30      | AR-15-FG-005428-01 |
| Caelo    | Betamethasone di... | 13236803         | 21366SI   | 31      | 20130730           |
| Euro OTC | Betamethasone di... | 1311023-01       | 21716SI   | 30      | 1505455            |
| Euro OTC | Betamethasone di... | 1601034          | 22372SI   | 30      | 20160204*          |
| Fagron   | Betamethasone di... | 16C04-B03-324513 | 22898SI   | 39      | 20160421           |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 390 spectra of 11 reference samples from the substance/substance group *Betamethasone dipropionate, micronized*. These samples are listed above in the [calibration samples](#) section.
- 70996 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 508 spectra of 16 reference samples from the substance/substance group *Betamethasone dipropionate, micronized*.

| Supplier | Substance                       | Batch      | Sample ID            | Spectra |
|----------|---------------------------------|------------|----------------------|---------|
| Fagron   | Betamethasone dipropionate, ... | 10K09-N06  | 20256                | 40      |
| Fagron   | Betamethasone dipropionate, ... | 13I17-N05  | 20952                | 80      |
| Caelo    | Betamethasone dipropionate, ... | 13236803   | 21367                | 35      |
| Euro OTC | Betamethasone dipropionate, ... | 1311023-01 | 21716 <sup>†</sup>   | 20      |
| Euro OTC | Betamethasone dipropionate, ... | 1601034    | 22372 <sup>†</sup>   | 15      |
| Euro OTC | Betamethasone dipropionate, ... | 1610014    | 22851                | 40      |
| Caelo    | Betamethasone dipropionate, ... | 171059     | 23342                | 40      |
| Euro OTC | Betamethasone dipropionate, ... | 1705020    | 23539                | 40      |
| Caelo    | Betamethasone dipropionate, ... | 13372501   | 21250SI <sup>†</sup> | 15      |
| Caelo    | Betamethasone dipropionate, ... | 13236803   | 21366SI <sup>†</sup> | 15      |
| Caelo    | Betamethasone dipropionate, ... | 13236803   | 21367SI              | 60      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

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| Supplier | Substance                       | Batch      | Sample ID            | Spectra |
|----------|---------------------------------|------------|----------------------|---------|
| Euro OTC | Betamethasone dipropionate, ... | 1311023-01 | 21716SI <sup>†</sup> | 16      |
| Euro OTC | Betamethasone dipropionate, ... | 1601034    | 22372SI <sup>†</sup> | 15      |
| Euro OTC | Betamethasone dipropionate, ... | 1610014    | 22851SI              | 30      |
| Caelo    | Betamethasone dipropionate, ... | 171059     | 23342SI              | 20      |
| Euro OTC | Betamethasone dipropionate, ... | 1705020    | 23539SI              | 27      |

- 146 221 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 307 spectra from 142 *Apo-Ident* customers from 91 batches from the substance/substance group *Betamethasone dipropionate, micronized*.

| Supplier            | Substance                       | Batch      | Spectra |
|---------------------|---------------------------------|------------|---------|
| Caelo               | Betamethasone dipropionate, ... | 3170717    | 1       |
| Caelo               | Betamethasone dipropionate, ... | 8K03-N13   | 2       |
| Fagron              | Betamethasone dipropionate, ... | 13/17-N05  | 11      |
|                     | Betamethasone dipropionate, ... | 13/17-N05  | 2       |
| Fagron              | Betamethasone dipropionate, ... | 13/17-n05  | 1       |
| Caelo               | Betamethasone dipropionate, ... | 13/17-N05  | 2       |
| Fargon/ Noweda      | Betamethasone dipropionate, ... | 13/17-N05  | 1       |
| Caelo               | Betamethasone dipropionate, ... | 1303006-01 | 1       |
| Euro OTC            | Betamethasone dipropionate, ... | 1305041-01 | 9       |
| Euro OTC            | Betamethasone dipropionate, ... | 1311023-01 | 6       |
| Euro OTC            | Betamethasone dipropionate, ... | 131102301  | 1       |
| Euro OTC            | Betamethasone dipropionate, ... | 1311023-02 | 5       |
| Fagron              | Betamethasone dipropionate, ... | 1317-N05   | 1       |
| Caelo               | Betamethasone dipropionate, ... | 13236801   | 6       |
| Caelo               | Betamethasone dipropionate, ... | 13236801ok | 1       |
| Caelo               | Betamethasone dipropionate, ... | 13236802   | 6       |
| Noweda              | Betamethasone dipropionate, ... | 13236803   | 1       |
| Caelo               | Betamethasone dipropionate, ... | 13236803   | 1       |
| Caelo               | Betamethasone dipropionate, ... | 13236805   | 5       |
| Phoenix 03.04.20147 | Betamethasone dipropionate, ... | 13236805   | 1       |
| Phoenix             | Betamethasone dipropionate, ... | 13236806   | 1       |
| Caelo               | Betamethasone dipropionate, ... | 13236806   | 4       |
| Caelo               | Betamethasone dipropionate, ... | 13372501   | 8       |
| Euro OTC            | Betamethasone dipropionate, ... | 13372501   | 1       |
| Caelo               | Betamethasone dipropionate, ... | 13372503   | 6       |
| Caelo               | Betamethasone dipropionate, ... | 13372504   | 6       |
| Caelo               | Betamethasone dipropionate, ... | 13372514   | 7       |
| Caelo               | Betamethasone dipropionate, ... | 13372515   | 3       |
| Caelo               | Betamethasone dipropionate, ... | 13372516   | 7       |
| Caelo               | Betamethasone dipropionate, ... | 13372520   | 2       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier                   | Substance                       | Batch            | Spectra |
|----------------------------|---------------------------------|------------------|---------|
| Fagron                     | Betamethasone dipropionate, ... | 13I17-N05        | 12      |
| Alliance health            | Betamethasone dipropionate, ... | 13I17-N05        | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 13j16-B01-291844 | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 13J16-B01-291844 | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 13J16-B01-291845 | 2       |
| Fagron                     | Betamethasone dipropionate, ... | 13j16-b01-291845 | 1       |
| Caelo                      | Betamethasone dipropionate, ... | 140507           | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 14C03-B06        | 2       |
| Fagron                     | Betamethasone dipropionate, ... | 14C03-B06-296837 | 4       |
| Anzag/fagromn              | Betamethasone dipropionate, ... | 14C03-B06-296837 | 1       |
| Euro OTC                   | Betamethasone dipropionate, ... | 1503003-01       | 3       |
| Caelo                      | Betamethasone dipropionate, ... | 1503003-01       | 2       |
| Euro OTC                   | Betamethasone dipropionate, ... | 1503003-02       | 6       |
| Euro/Sanacorp              | Betamethasone dipropionate, ... | 1503003-02       | 1       |
| Caelo                      | Betamethasone dipropionate, ... | 1503003-02       | 1       |
| Euro OTC                   | Betamethasone dipropionate, ... | 150300302        | 1       |
| Euro OTC                   | Betamethasone dipropionate, ... | 1506016-02       | 1       |
| Caelo                      | Betamethasone dipropionate, ... | 15163301         | 16      |
| Caelo                      | Betamethasone dipropionate, ... | 15163302         | 2       |
| Caelo                      | Betamethasone dipropionate, ... | 15163303         | 9       |
| Caelo                      | Betamethasone dipropionate, ... | 15163304         | 4       |
| Caelo                      | Betamethasone dipropionate, ... | 15238701         | 8       |
| Gehe                       | Betamethasone dipropionate, ... | 15238701         | 1       |
| Caelo                      | Betamethasone dipropionate, ... | 15412906         | 5       |
| Caelo                      | Betamethasone dipropionate, ... | 15412907         | 3       |
| Caelo                      | Betamethasone dipropionate, ... | 15412910         | 2       |
| Fagron                     | Betamethasone dipropionate, ... | 15H25-B06-313088 | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 15H28-B06-313088 | 1       |
| Euro OTC                   | Betamethasone dipropionate, ... | 160103401        | 1       |
| Euro OTC                   | Betamethasone dipropionate, ... | 1601034-01       | 13      |
| Euro OTC                   | Betamethasone dipropionate, ... | 1610014-01       | 5       |
| Fagron                     | Betamethasone dipropionate, ... | 16C04-B03-320850 | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 2109DM0          | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 2109DM0B0011322  | 1       |
| Caelo                      | Betamethasone dipropionate, ... | 2109DM0B0011322  | 1       |
| Sanacorp                   | Betamethasone dipropionate, ... |                  | 1       |
| Euro OTC                   | Betamethasone dipropionate, ... | Co0044/1A15020   | 1       |
| Phönix Gotha               | Betamethasone dipropionate, ... | 11/02-N01        | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 11I02-N01        | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 11K28-N10        | 4       |
| Fagron                     | Betamethasone dipropionate, ... | 9J05-N09         | 1       |
| Caelo                      | Betamethasone dipropionate, ... |                  | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 10E19-N03        | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 11D26-N06        | 2       |
| Caelo                      | Betamethasone dipropionate, ... | 1210020-01       | 1       |
| Caelo                      | Betamethasone dipropionate, ... | 12114501         | 1       |
| Euro OTC                   | Betamethasone dipropionate, ... | 121002001        | 1       |
| Phönix 05.12.12            | Betamethasone dipropionate, ... | 12114505         | 1       |
| Caelo                      | Betamethasone dipropionate, ... | 12114506         | 1       |
| Caelo                      | Betamethasone dipropionate, ... | 12114507         | 3       |
| Noweda                     | Betamethasone dipropionate, ... | 12114509         | 1       |
| Caesar/Lorenz              | Betamethasone dipropionate, ... | 12114509         | 1       |
| Caelo                      | Betamethasone dipropionate, ... | 12114511         | 2       |
| Caelo                      | Betamethasone dipropionate, ... | 12114512         | 1       |
| Caelo                      | Betamethasone dipropionate, ... | 12114513         | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 12827-N08        | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 12B27-N08        | 4       |
| Bombastus                  | Betamethasone dipropionate, ... | 12B27N08         | 1       |
| Fagron                     | Betamethasone dipropionate, ... | 12C21-N13        | 1       |
| Alliance Health 24.01.2... | Betamethasone dipropionate, ... | 13/17-N05        | 1       |

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| Supplier       | Substance                       | Batch       | Spectra |
|----------------|---------------------------------|-------------|---------|
| Caelo          | Betamethasone dipropionate, ... | 13023001    | 3       |
| Caelo          | Betamethasone dipropionate, ... | 13023002    | 6       |
| Fagron         | Betamethasone dipropionate, ... | 13023004    | 1       |
| Caelo          | Betamethasone dipropionate, ... | 13023005    | 8       |
| Euro OTC       | Betamethasone dipropionate, ... | 1303006/01  | 1       |
| Hirsch         | Betamethasone dipropionate, ... | 1303006-01  | 1       |
| Euro OTC       | Betamethasone dipropionate, ... | 1303006-02  | 1       |
| Fagron         | Betamethasone dipropionate, ... | 1303006-02  | 1       |
| Phönix         | Betamethasone dipropionate, ... | 1303006-02  | 1       |
| Euro OTC       | Betamethasone dipropionate, ... | 1305041-02  | 2       |
| Caelo/Sanacorp | Betamethasone dipropionate, ... | 13125701    | 1       |
| Caelo          | Betamethasone dipropionate, ... | 13125701    | 3       |
| Caelo          | Betamethasone dipropionate, ... | 13125703    | 4       |
| Euro OTC       | Betamethasone dipropionate, ... | 13125702    | 1       |
| Fagron         | Betamethasone dipropionate, ... |             | 1       |
| Noweda         | Betamethasone dipropionate, ... | 13236802    | 1       |
| Caelo          | Betamethasone dipropionate, ... | 1325702     | 1       |
| Caelo          | Betamethasone dipropionate, ... | 18121306    | 1       |
| Caelo          | Betamethasone dipropionate, ... | 2313A-03644 | 1       |
| Caelo          | Betamethasone dipropionate, ... | AKD11       | 1       |
| Anzag          | Betamethasone dipropionate, ... | 12114513    | 2       |
| Euro OTC       | Betamethasone dipropionate, ... | 1303006-01  | 1       |
| EUro/AHD       | Betamethasone dipropionate, ... | 1303006-01  | 3       |
| Euro OTC       | Betamethasone dipropionate, ... | 130541-01   | 1       |

- 69 326 spectra from 414 *Apo-Ident* customers from a total of 23 713 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Betamethasone dipropionate, micronized* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Betamethasone dipropionate, micronized* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 390           | 0              | 70 996        |
| <b>Type B</b> | 0              | 508           | 0              | 146 221       |
| <b>Type C</b> | 0              | 305           | 2              | 69 326        |

The substance/substance group *Betamethasone dipropionate, micronized* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.4615 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.8189 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 99.3485 % (> 98.3713 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20930     | 20930               | 0.00                         | 11.47                           |
| 21250     | 21250               | 0.00                         | 10.84                           |
| 21366     | 20930               | 5.43                         | 14.99                           |
| 21716     | 21716               | 0.00                         | 8.65                            |
| 22372     | 22372               | 0.00                         | 11.55                           |
| 22898     | 20930               | 4.62                         | 12.88                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Betamethasone valerate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20026-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Betamethasone valerate; Betamethasoni valeras; Betamethasonum valerianicum

### Special notes

When selecting the *Betamethasone valerate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Betamethasone valerate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Betamethasone va... | 12K07-N23        | 20887     | 39      | 20121119    |
| Euro OTC | Betamethasone va... | 1208014-01       | 20920     | 40      | 20120928    |
| Caelo    | Betamethasone va... | 13091213         | 21215     | 40      | 20130506    |
| Fagron   | Betamethasone va... | 13K29-B32-288243 | 21566     | 40      | 20131210    |
| Caelo    | Betamethasone va... | 13225507         | 21588     | 34      | 1706018     |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Betamethasone va... | 1406019-01       | 21645     | 40      | 20140725    |
| Fagron   | Betamethasone va... | 13K05-B08-292651 | 21674     | 40      | 1511154     |
| Euro OTC | Betamethasone va... | 1510037          | 22249     | 40      | 20151215*   |
| Euro OTC | Betamethasone va... | 1610010          | 22861     | 40      | 20161116*   |
| Euro OTC | Betamethasone va... | 1510037          | 22249SI   | 20      | 20151215*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 373 spectra of 10 reference samples from the substance/substance group *Betamethasone valerate*. These samples are listed above in the [calibration samples](#) section.
- 71 013 spectra from a total of 1543 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 429 spectra of 16 reference samples from the substance/substance group *Betamethasone valerate*.

| Supplier | Substance              | Batch            | Sample ID            | Spectra |
|----------|------------------------|------------------|----------------------|---------|
| Caelo    | Betamethasone valerate | 82806109         | 20026                | 30      |
| Fagron   | Betamethasone valerate | 13K29-B32-288243 | 21566 <sup>†</sup>   | 20      |
| Caelo    | Betamethasone valerate | 13225507         | 21588 <sup>†</sup>   | 26      |
| Euro OTC | Betamethasone valerate | 1406019-01       | 21645 <sup>†</sup>   | 20      |
| Fagron   | Betamethasone valerate | 13K05-B08-292651 | 21674 <sup>†</sup>   | 20      |
| Euro OTC | Betamethasone valerate | 1510037          | 22249 <sup>†</sup>   | 20      |
| Euro OTC | Betamethasone valerate | 1606023          | 22716                | 40      |
| Caelo    | Betamethasone valerate | 170787           | 23332                | 40      |
| Euro OTC | Betamethasone valerate | 1704019          | 23396                | 40      |
| Caelo    | Betamethasone valerate | 172716           | 23683                | 30      |
| Euro OTC | Betamethasone valerate | 1510037          | 22249SI <sup>†</sup> | 10      |
| Euro OTC | Betamethasone valerate | 1606023          | 22716SI              | 34      |
| Euro OTC | Betamethasone valerate | 1610010          | 22861SI              | 30      |
| Caelo    | Betamethasone valerate | 170787           | 23332SI              | 20      |
| Euro OTC | Betamethasone valerate | 1704019          | 23396SI              | 29      |
| Caelo    | Betamethasone valerate | 172716           | 23683SI              | 20      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.



- 146 300 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1278 spectra from 311 *Apo-Ident* customers from 292 batches from the substance/substance group *Betamethasone valerate*.

| Supplier                   | Substance              | Batch            | Spectra |
|----------------------------|------------------------|------------------|---------|
| Caelo                      | Betamethasone valerate | 8081502          | 1       |
| Caelo                      | Betamethasone valerate | 10106313         | 1       |
| Caelo                      | Betamethasone valerate | 12003403         | 10      |
| Euro OTC                   | Betamethasone valerate | 1208014-01       | 18      |
| Fagron                     | Betamethasone valerate | 11E18-N03        | 4       |
| Caelo                      | Betamethasone valerate | 10296707         | 1       |
| Caesar & Loretz GmbH Hi... | Betamethasone valerate | 120801402        | 1       |
| Euro OTC                   | Betamethasone valerate | 1208014-03       | 5       |
| Euro OTC                   | Betamethasone valerate | 1208014-04       | 8       |
| Symbolica Spec/Noweda      | Betamethasone valerate | 1208014-04       | 1       |
| Caelo                      | Betamethasone valerate | 123345           | 1       |
| Fagron                     | Betamethasone valerate | 12K07-N23        | 8       |
| Fagron                     | Betamethasone valerate | 12K07N23         | 1       |
| Fagron                     | Betamethasone valerate | 12L11-N01        | 17      |
| Fagron                     | Betamethasone valerate | 12L11-N01        | 2       |
| Fagron                     | Betamethasone valerate | 13/17-B08-292649 | 2       |
| Caelo                      | Betamethasone valerate | 13012015C        | 1       |
| Caelo                      | Betamethasone valerate | 13091203         | 15      |
| Caelo                      | Betamethasone valerate | 13091205         | 12      |
| AHD 17.11.14 EK 18,11      | Betamethasone valerate | 13091205         | 1       |
| Noweda                     | Betamethasone valerate | 13091205         | 1       |
| Caelo                      | Betamethasone valerate | 13091206         | 2       |
| Caelo                      | Betamethasone valerate | 13091207         | 9       |
| Phönix                     | Betamethasone valerate | 13091209         | 2       |
| Caelo                      | Betamethasone valerate | 13091209         | 6       |
| Gehe 13.02.14              | Betamethasone valerate | 13091210         | 3       |
| Caelo                      | Betamethasone valerate | 13091211         | 3       |
| Caelo                      | Betamethasone valerate | 13091212         | 9       |
| Caelo                      | Betamethasone valerate | 13091213         | 8       |
| Phönix Gotha               | Betamethasone valerate | 13091213         | 1       |
| Euro OTC                   | Betamethasone valerate | 1311039          | 1       |
| Euro OTC                   | Betamethasone valerate | 1311039-01       | 21      |
| Euro OTC                   | Betamethasone valerate | 131103901        | 1       |
| Noveda                     | Betamethasone valerate | 1311039-01       | 1       |
| Fagron                     | Betamethasone valerate | 1311039-01       | 1       |
| NEWCHEM                    | Betamethasone valerate | 1311039-01       | 1       |
| Euro OTC                   | Betamethasone valerate | 131139-01        | 1       |
| Caelo                      | Betamethasone valerate | 13225502         | 3       |
| Caelo                      | Betamethasone valerate | 13225503         | 8       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier               | Substance              | Batch            | Spectra |
|------------------------|------------------------|------------------|---------|
| GEHE 17.06.2014        | Betamethasone valerate | 13225503         | 1       |
| Caelo                  | Betamethasone valerate | 13225504         | 10      |
| Caesar & Loretz GmbH   | Betamethasone valerate | 13225504         | 1       |
| Caelo                  | Betamethasone valerate | 13225505         | 8       |
| Caelo                  | Betamethasone valerate | 13225507         | 2       |
| Caelo                  | Betamethasone valerate | 13225508         | 11      |
| Phoenix Goettin        | Betamethasone valerate | 13225508         | 1       |
| Hustadt Apotheke       | Betamethasone valerate | 13225508         | 1       |
| Caelo                  | Betamethasone valerate | 13225509         | 2       |
| Caelo                  | Betamethasone valerate | 13225515         | 9       |
| Caelo                  | Betamethasone valerate | 13225516         | 9       |
| AHDE / Cael 17.02.2015 | Betamethasone valerate | 13225516         | 1       |
| Caelo                  | Betamethasone valerate | 13225607         | 1       |
| Fagron                 | Betamethasone valerate | 13D03-N07        | 45      |
| Fagron                 | Betamethasone valerate | 13G19-N01        | 49      |
| Fargon/Anzag           | Betamethasone valerate | 13G19-N01        | 1       |
| Herbasinica            | Betamethasone valerate | 13g19-n01        | 1       |
| Caelo                  | Betamethasone valerate | 13G19-N01        | 2       |
| Fargon/Alliance HC     | Betamethasone valerate | 13G19-N01        | 2       |
| Fagron                 | Betamethasone valerate | 13g19-n01        | 2       |
| Hirsch                 | Betamethasone valerate | 13G19-No1        | 1       |
| Fagron                 | Betamethasone valerate | 13K05-B08        | 4       |
| Fagron                 | Betamethasone valerate | 13K05-B08-092652 | 1       |
| Fagron                 | Betamethasone valerate | 13K05-B08-291663 | 1       |
| Fagron                 | Betamethasone valerate | 13K05-B08-292647 | 3       |
| Fagron                 | Betamethasone valerate | 13K29-B12-288247 | 1       |
| Fagron                 | Betamethasone valerate | 13K29-B23-288246 | 1       |
| Fagron                 | Betamethasone valerate | 13K29-B32        | 7       |
| Fagron                 | Betamethasone valerate | 13K05-B08-292652 | 1       |
| Fagron                 | Betamethasone valerate | 13K29-B32-28824  | 1       |
| Fagron                 | Betamethasone valerate | 13K29B32288243   | 1       |
| Fagron                 | Betamethasone valerate | 13K29-B32-288244 | 1       |
| Fagron                 | Betamethasone valerate | 13K29-B32-288246 | 4       |
| Fagron                 | Betamethasone valerate | 13K29-B32-288245 | 1       |
| Fagron                 | Betamethasone valerate | 13K29-B32-288247 | 16      |
| Ichthyol-Gesellschaft  | Betamethasone valerate | 13k29-B32-288247 | 1       |
| Caelo                  | Betamethasone valerate | 13K29-B32-288247 | 1       |
| Fargon/Alliance HC     | Betamethasone valerate | 13K29-B32-288247 | 1       |
| Caelo                  | Betamethasone valerate | 13K29B32288247   | 1       |
| Fagron                 | Betamethasone valerate | 13k29b32288247   | 1       |
| Fagron                 | Betamethasone valerate | 13K29-B32-288248 | 3       |
| Fagron                 | Betamethasone valerate | 13K29-B32-288250 | 3       |
| Fargon                 | Betamethasone valerate | 13k29-b32-289364 | 1       |
| Euro OTC               | Betamethasone valerate | 13K29-B32-289364 | 1       |
| Fagron                 | Betamethasone valerate | 13117-B08-292649 | 2       |
| Caelo                  | Betamethasone valerate | 14031407         | 1       |
| Euro OTC               | Betamethasone valerate | 1406011903       | 1       |
| Euro OTC               | Betamethasone valerate | 1406019-01       | 24      |
| Symbiotica Spec.       | Betamethasone valerate | 1406019-01       | 3       |
| Euro OTC               | Betamethasone valerate | 140601901        | 1       |
| noweda                 | Betamethasone valerate | 1406019-01       | 1       |
| Euro OTC               | Betamethasone valerate | 1406019-02       | 22      |
| AHD                    | Betamethasone valerate | 1406019-02       | 2       |
| Euro OTC               | Betamethasone valerate | 140601902        | 1       |
| Caelo                  | Betamethasone valerate | 1406019-02       | 1       |
| EuRho                  | Betamethasone valerate | 1406019-02       | 1       |
| Euro OTC               | Betamethasone valerate | 1406019-03       | 23      |
| Euro OTC               | Betamethasone valerate | 140601903        | 2       |
| Caelo                  | Betamethasone valerate | 1406019-03       | 2       |
| Euroo                  | Betamethasone valerate | 1406019-03       | 1       |

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| <b>Supplier</b>           | <b>Substance</b>       | <b>Batch</b>      | <b>Spectra</b> |
|---------------------------|------------------------|-------------------|----------------|
| Caelo                     | Betamethasone valerate | 140601903         | 1              |
| Fagron                    | Betamethasone valerate | 1406019-03        | 1              |
| Noweda                    | Betamethasone valerate | 1406019-03        | 1              |
| Caelo                     | Betamethasone valerate | 14188602          | 4              |
| Caelo                     | Betamethasone valerate | 14188603          | 5              |
| Fagron                    | Betamethasone valerate | 14188603          | 1              |
| Caelo                     | Betamethasone valerate | 14188604          | 8              |
| Phönix Gotha              | Betamethasone valerate | 14188608          | 1              |
| caesar&lorenz,phönix      | Betamethasone valerate | 14188606          | 1              |
| Caelo                     | Betamethasone valerate | 14188608          | 5              |
| Caelo                     | Betamethasone valerate | 14188609          | 3              |
| Caelo                     | Betamethasone valerate | 14188610          | 5              |
| Caelo                     | Betamethasone valerate | 14188617          | 1              |
| Caelo                     | Betamethasone valerate | 14188619          | 3              |
| Alliance Healthcare       | Betamethasone valerate | 146019-02         | 1              |
| Caelo                     | Betamethasone valerate | 1488610           | 1              |
| Fagron                    | Betamethasone valerate | 14C19-B02         | 3              |
| Fagron                    | Betamethasone valerate | 14C19B02          | 1              |
| Fagron                    | Betamethasone valerate | 14C19-B02-292646  | 1              |
| Fagron                    | Betamethasone valerate | 14C19-B02-292648  | 1              |
| Fagron                    | Betamethasone valerate | 14C19-B02-292650  | 3              |
| Fagron                    | Betamethasone valerate | 14c19-b02-292650  | 1              |
| Fagron                    | Betamethasone valerate | 14C19-B02-292653  | 6              |
| Caelo                     | Betamethasone valerate | 14C19-B02-292653  | 1              |
| Fagron                    | Betamethasone valerate | 14C19-B02-2926550 | 1              |
| Fagron                    | Betamethasone valerate | 14C19-B02-296168  | 2              |
| Fagron                    | Betamethasone valerate | 14C19-B02-296169  | 2              |
| Fagron                    | Betamethasone valerate | 14G30-B05         | 7              |
| Caelo                     | Betamethasone valerate | 14G30-B05         | 1              |
| Fagron                    | Betamethasone valerate | 14G30-B05-296172  | 3              |
| Fagron                    | Betamethasone valerate | 14G30-B05-296173  | 9              |
| Fagron                    | Betamethasone valerate | 14G30-B05-296175  | 1              |
| Fagron                    | Betamethasone valerate | 14G30-B05-309518  | 1              |
| Fagron                    | Betamethasone valerate | 14G30B05309519    | 1              |
| Fagron                    | Betamethasone valerate | 14G30-B05-309520  | 4              |
| Fagron                    | Betamethasone valerate | 14G30-B05-309521  | 1              |
| Fagron                    | Betamethasone valerate | 14H28-B01         | 3              |
| Fagron                    | Betamethasone valerate | 14H28B01          | 1              |
| Fagron                    | Betamethasone valerate | 14H28-B01-302683  | 1              |
| Fagron                    | Betamethasone valerate | 14H28-B01-302863  | 3              |
| Fagron                    | Betamethasone valerate | 14H28-B01-302864  | 4              |
| Cael Sanacorp 05.02.2016  | Betamethasone valerate | 14H28-B01-302864  | 1              |
| Fagron                    | Betamethasone valerate | 14H28-B01-302865  | 13             |
| Caelo                     | Betamethasone valerate | 14H28-B01-302865  | 1              |
| Fagron                    | Betamethasone valerate | 14h28-b01-302865  | 2              |
| Fagron                    | Betamethasone valerate | 14H28-B01-302866  | 3              |
| Fagron                    | Betamethasone valerate | 14H28-b01-302866  | 1              |
| Fagron,VDL;4.1.15; 106,74 | Betamethasone valerate | 14H28-B01-302866  | 1              |
| Hedinger                  | Betamethasone valerate | 14H28-B01-302877  | 1              |
| Fagron                    | Betamethasone valerate | 14H28-B01-302877  | 2              |
| Fagron                    | Betamethasone valerate | 14H28-B01-305470  | 1              |
| AHD/Fargon                | Betamethasone valerate | 14H28-Bo1-302865  | 1              |
| Fagron                    | Betamethasone valerate | 15/16-B07317428   | 1              |
| Fagron                    | Betamethasone valerate | 15/16-B07-317416  | 2              |
| Ebert u. Jacobi 16.0...   | Betamethasone valerate | 15/16-B07-317417  | 1              |
| Fagron                    | Betamethasone valerate | 15/16-B07-317417  | 1              |
| Fagron                    | Betamethasone valerate | 15/16-B07-317428  | 1              |
| Caelo                     | Betamethasone valerate | 15/16-B07-319228  | 2              |
| Fagron                    | Betamethasone valerate | 15/16-B07-319228  | 1              |
| Caelo                     | Betamethasone valerate | 15075802          | 16             |

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| Supplier                   | Substance              | Batch            | Spectra |
|----------------------------|------------------------|------------------|---------|
| Allianz Healthcare 27.0... | Betamethasone valerate | 15075802         | 1       |
| Caesar&Loretz GmbH/Anzag   | Betamethasone valerate | 15075802         | 1       |
| Fagron                     | Betamethasone valerate | 15075802         | 1       |
| Caelo                      | Betamethasone valerate | 15075803         | 6       |
| Caelo/Sanacorp             | Betamethasone valerate | 15075803         | 1       |
| Caesar und Loretz          | Betamethasone valerate | 15075803         | 1       |
| Caelo                      | Betamethasone valerate | 150758036        | 1       |
| Caelo                      | Betamethasone valerate | 15075804         | 9       |
| Caelo                      | Betamethasone valerate | 15075805         | 4       |
| Caelo                      | Betamethasone valerate | 15075809         | 1       |
| Caelo                      | Betamethasone valerate | 15075810         | 4       |
| Noweda                     | Betamethasone valerate | 15075812         | 1       |
| Caelo                      | Betamethasone valerate | 15075812         | 3       |
| Bombastus                  | Betamethasone valerate | 1510037-01       | 1       |
| Euro OTC                   | Betamethasone valerate | 1510037-01       | 11      |
| Euro/Alliance Healthcare   | Betamethasone valerate | 1510037-01       | 1       |
| Caelo                      | Betamethasone valerate | 1510037-01       | 1       |
| Fagron                     | Betamethasone valerate | 15116-B07        | 1       |
| Fagron                     | Betamethasone valerate | 1516-B07-317416  | 1       |
| Fagron                     | Betamethasone valerate | 1516-B07-317417  | 1       |
| Caelo                      | Betamethasone valerate | 1516-B07-319228  | 1       |
| Caelo                      | Betamethasone valerate | 15262602         | 3       |
| Caelo                      | Betamethasone valerate | 15262603         | 10      |
| Caelo                      | Betamethasone valerate | 15262604         | 8       |
| Caelo                      | Betamethasone valerate | 15262606         | 2       |
| Caelo                      | Betamethasone valerate | 15262607         | 6       |
| Caelo                      | Betamethasone valerate | 15262609         | 2       |
| Caelo                      | Betamethasone valerate | 15262610         | 3       |
| Caelo                      | Betamethasone valerate | 15398501         | 11      |
| Euro OTC                   | Betamethasone valerate | 15398501         | 1       |
| Gehe                       | Betamethasone valerate | 15398501         | 1       |
| Caelo                      | Betamethasone valerate | 15398503         | 1       |
| AHD 15.06.16 EK:18,44      | Betamethasone valerate | 15398505         | 1       |
| Caelo                      | Betamethasone valerate | 15398505         | 4       |
| Caelo                      | Betamethasone valerate | 15398506         | 12      |
| Caelo                      | Betamethasone valerate | 15398512         | 5       |
| Caelo                      | Betamethasone valerate | 15398514         | 1       |
| Caelo                      | Betamethasone valerate | 15398515         | 9       |
| Fagron                     | Betamethasone valerate | 15824-B04        | 1       |
| Fagron                     | Betamethasone valerate | 15B24-B04        | 2       |
| Caelo                      | Betamethasone valerate | 15B24-B04        | 1       |
| Fagron                     | Betamethasone valerate | 15B24-B04-307015 | 1       |
| Fagron                     | Betamethasone valerate | 15B24-B04-307016 | 8       |
| Caelo                      | Betamethasone valerate | 15B24-B04-307016 | 1       |
| Fagron                     | Betamethasone valerate | 15F16-B04        | 3       |
| Fagron                     | Betamethasone valerate | 15F16-B04-314054 | 1       |
| Fagron                     | Betamethasone valerate | 15F16-B04-314882 | 1       |
| Fagron                     | Betamethasone valerate | 15f16-b04314054  | 1       |
| Fagron                     | Betamethasone valerate | 15F16-B04-315328 | 1       |
| Fagron                     | Betamethasone valerate | 15I16-B07        | 1       |
| Fagron                     | Betamethasone valerate | 15I16-B07-317416 | 1       |
| Fagron                     | Betamethasone valerate | 15I16-B07-317417 | 1       |
| Fagron                     | Betamethasone valerate | 15I16-B07-319228 | 1       |
| Fagron                     | Betamethasone valerate | 15I16-B07-319832 | 2       |
| Fagron                     | Betamethasone valerate | 15I16-Bo7-319832 | 1       |
| Caelo                      | Betamethasone valerate | 15L21-B03-318663 | 1       |
| Euro OTC                   | Betamethasone valerate | 1606023-01       | 14      |
| Euro OTC                   | Betamethasone valerate | 1610010-01       | 11      |
| Caelo                      | Betamethasone valerate | 1610010-01       | 1       |
| Caelo                      | Betamethasone valerate | 16270501         | 6       |

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| <b>Supplier</b>            | <b>Substance</b>       | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------------|------------------|----------------|
| Caelo                      | Betamethasone valerate | 16270502         | 9              |
| Caelo                      | Betamethasone valerate | 16270503         | 3              |
| Gehe                       | Betamethasone valerate | 16270505         | 1              |
| Caelo                      | Betamethasone valerate | 16270505         | 2              |
| Caelo                      | Betamethasone valerate | 16270509         | 1              |
| Caelo/Noweda               | Betamethasone valerate | 16270509         | 2              |
| Caesar&Loretz GmbH,PHön... | Betamethasone valerate | 16270509         | 1              |
| Caelo                      | Betamethasone valerate | 1627051          | 1              |
| Caelo                      | Betamethasone valerate | 16270511         | 1              |
| Fagron                     | Betamethasone valerate | 16270513         | 1              |
| Caelo                      | Betamethasone valerate | 16270513         | 1              |
| Caelo                      | Betamethasone valerate | 16270513         | 1              |
| Fargon/Anzag               | Betamethasone valerate | 16B18-B02-320971 | 1              |
| Fagron                     | Betamethasone valerate | 16B18-B02-320971 | 2              |
| Caelo                      | Betamethasone valerate | 16B18-B02-320971 | 1              |
| Fagron                     | Betamethasone valerate | 16B18-B02320971  | 1              |
| Fagron                     | Betamethasone valerate | 16B18-B02-322109 | 1              |
| Fargon/Alliance HC         | Betamethasone valerate | 16B18-B02-322111 | 1              |
| Fagron                     | Betamethasone valerate | 16B18-B02-322111 | 1              |
| Caelo                      | Betamethasone valerate | 16B18-B02-322121 | 2              |
| Fagron                     | Betamethasone valerate | 16B18-B02-323034 | 3              |
| Fagron                     | Betamethasone valerate | 16b18-b02-324798 | 1              |
| Caelo                      | Betamethasone valerate | 16E23-B03        | 1              |
| Fagron                     | Betamethasone valerate | 16E23-B03-324799 | 2              |
| Caelo                      | Betamethasone valerate | 16E23-B03-324799 | 1              |
| Fagron                     | Betamethasone valerate | 16E23-B03-324800 | 2              |
| Caelo                      | Betamethasone valerate | 16E23-B03-324800 | 1              |
| Fagron                     | Betamethasone valerate | 16E23-B03-327354 | 1              |
| Fagron                     | Betamethasone valerate | 16E23-B03-328128 | 4              |
| Fagron                     | Betamethasone valerate | 16E23B03328128   | 1              |
| Fagron                     | Betamethasone valerate | 16H22-B06        | 1              |
| Fagron                     | Betamethasone valerate | 16H22-B06329223  | 1              |
| Euro OTC                   | Betamethasone valerate | 1704019-01       | 2              |
| Caelo                      | Betamethasone valerate | 17078701         | 1              |
| Gehe                       | Betamethasone valerate | 1712E-01181      | 1              |
| Caelo                      | Betamethasone valerate | 18071403         | 1              |
| Euro OTC                   | Betamethasone valerate | 2014Q1181        | 1              |
| Fagron                     | Betamethasone valerate | 2186             | 1              |
| Fagron                     | Betamethasone valerate | 292652           | 1              |
| Fagron                     | Betamethasone valerate | 700103-0004      | 1              |
| Fagron                     | Betamethasone valerate | BV019/0514       | 1              |
| Fagron                     | Betamethasone valerate | BV036/1215       | 1              |
| Fagron                     | Betamethasone valerate | BV-BLT225/0514   | 1              |
| Caelo                      | Betamethasone valerate | BV-BLT225/0514   | 1              |
| Fragron                    | Betamethasone valerate | BV-BLT225/0514   | 2              |
| Galderma/ Noweda           | Betamethasone valerate | C0023/115040     | 1              |
| Oberlinden Apotheke        | Betamethasone valerate | C0073/115040     | 3              |
| Caelo                      | Betamethasone valerate | C0073/1          | 3              |
| Oberlinden Apotheke        | Betamethasone valerate | c073/115040      | 1              |
| Sanacorp                   | Betamethasone valerate |                  | 1              |
| Fagron                     | Betamethasone valerate | NT0597M          | 2              |
| Caelo                      | Betamethasone valerate | NT0597M          | 1              |
| Fagron                     | Betamethasone valerate | 612211181        | 1              |
| Caelo                      | Betamethasone valerate | 10296701         | 1              |
| Caelo                      | Betamethasone valerate | 10296705         | 2              |
| Euro OTC                   | Betamethasone valerate | 110804-02        | 1              |
| Euro OTC                   | Betamethasone valerate | 1108045-01       | 3              |
| Euro/Gehe                  | Betamethasone valerate | 1108045-02       | 1              |
| Caelo                      | Betamethasone valerate | 1108045-03       | 6              |
| Kehr                       | Betamethasone valerate | 1108045-03       | 1              |

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| <b>Supplier</b>            | <b>Substance</b>       | <b>Batch</b> | <b>Spectra</b> |
|----------------------------|------------------------|--------------|----------------|
| Euro OTC                   | Betamethasone valerate | 1108045-03   | 8              |
| Caelo                      | Betamethasone valerate | 1113         | 1              |
| Noweda                     | Betamethasone valerate | 11131902     | 1              |
| Caelo                      | Betamethasone valerate | 11131905     | 1              |
| Caelo                      | Betamethasone valerate | 11131909     | 1              |
| Caelo                      | Betamethasone valerate | 11131906     | 2              |
| Caesar & Loretz GmbH, 4... | Betamethasone valerate | 11131914     | 3              |
| Caelo                      | Betamethasone valerate | 11131914     | 2              |
| Caelo                      | Betamethasone valerate | 11131917     | 4              |
| Caesar & Loretz GmbH       | Betamethasone valerate | 11131917     | 1              |
| Caelo                      | Betamethasone valerate | 1131914      | 1              |
| Noweda                     | Betamethasone valerate | 11K18-N09    | 1              |
| Fagron                     | Betamethasone valerate | 11K18-N09    | 4              |
| Gehe                       | Betamethasone valerate | 12003403     | 2              |
| Phönix Gotha               | Betamethasone valerate | 12003403     | 1              |
| Caesar/Lorenz              | Betamethasone valerate | 12003403     | 1              |
| Caelo                      | Betamethasone valerate | 12003404     | 4              |
| Caesar & Loretz GmbH, 4... | Betamethasone valerate | 12003404     | 1              |
| Caelo                      | Betamethasone valerate | 12003405     | 8              |
| Anzag 24.10.12             | Betamethasone valerate | 12003405     | 1              |
| Phönix Gotha               | Betamethasone valerate | 12003405     | 1              |
| Caelo                      | Betamethasone valerate | 12003406     | 8              |
| Caelo                      | Betamethasone valerate | 12003407     | 1              |
| Gehe                       | Betamethasone valerate | 12003409     | 1              |
| Caesar & Loretz GmbH, 4... | Betamethasone valerate | 12003409     | 2              |
| Caelo                      | Betamethasone valerate | 12003409     | 2              |
| Phoenix                    | Betamethasone valerate | 12003409     | 2              |
| Caelo                      | Betamethasone valerate | 12003410     | 2              |
| Caelo                      | Betamethasone valerate | 12003411     | 4              |
| vdl                        | Betamethasone valerate | 12003411     | 1              |
| Kehr                       | Betamethasone valerate | 1208014-01   | 1              |
| Euro OTC                   | Betamethasone valerate | 120801401    | 1              |
| Caelo                      | Betamethasone valerate | 120801401    | 1              |
| GEHE                       | Betamethasone valerate | 1208014-02   | 1              |
| Euro OTC                   | Betamethasone valerate | 1208014-02   | 11             |
| Noweda                     | Betamethasone valerate | 1208014-02   | 2              |
| Euro OTC                   | Betamethasone valerate | 120801402    | 2              |
| Fagron                     | Betamethasone valerate | 120801402    | 1              |
| Symbiotica Spec.           | Betamethasone valerate | 1208014-04   | 1              |
| Euro OTC                   | Betamethasone valerate | 120801404    | 1              |
| Euro OTC                   | Betamethasone valerate | 120812-02    | 1              |
| Caelo                      | Betamethasone valerate | 12229802     | 5              |
| Caelo                      | Betamethasone valerate | 12229804     | 5              |
| Gehe                       | Betamethasone valerate | 12229804     | 1              |
| Caelo                      | Betamethasone valerate | 12229805     | 10             |
| Caelo                      | Betamethasone valerate | 12229806     | 7              |
| Phönix                     | Betamethasone valerate | 12229807     | 1              |
| Caelo                      | Betamethasone valerate | 12229808     | 11             |
| Ph.Eur.7,0                 | Betamethasone valerate | 12229808     | 1              |
| Phönix Gotha               | Betamethasone valerate | 12229808     | 1              |
| Caelo                      | Betamethasone valerate | 12229809     | 2              |
| Caesar & Loretz GmbH, 4... | Betamethasone valerate | 12229809     | 1              |
| Gehe                       | Betamethasone valerate | 12229809     | 1              |
| Caelo                      | Betamethasone valerate | 12229810     | 3              |
| Caelo                      | Betamethasone valerate | 12229811     | 7              |
| Caelo                      | Betamethasone valerate | 12229812     | 13             |
| Caelo                      | Betamethasone valerate | 12229813     | 2              |
| GEHE                       | Betamethasone valerate | 12229813     | 1              |
| Noweda                     | Betamethasone valerate | 12229832     | 1              |
| Großhandel                 | Betamethasone valerate | 12B028-N01   | 1              |

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| <b>Supplier</b>            | <b>Substance</b>       | <b>Batch</b>    | <b>Spectra</b> |
|----------------------------|------------------------|-----------------|----------------|
| Fagron                     | Betamethasone valerate | 12B28-N01       | 9              |
| phönix, 12.12.12           | Betamethasone valerate | 12B28-N01       | 4              |
| Noweda                     | Betamethasone valerate | 12B28-N01       | 2              |
| FARGON                     | Betamethasone valerate | 12g09-n07       | 2              |
| Fagron                     | Betamethasone valerate | 12G09-N07       | 25             |
| Caelo                      | Betamethasone valerate | 12G09-N07       | 3              |
| Sanacorp                   | Betamethasone valerate | 12G09-N07       | 1              |
| Noweda                     | Betamethasone valerate | 12G09-N07       | 4              |
| AHC 01.07.13 EK 48,05      | Betamethasone valerate | 12K07-N23       | 1              |
| Caelo                      | Betamethasone valerate | 12L11-N01       | 3              |
| Bombastus                  | Betamethasone valerate | 12L11-N01       | 1              |
| Ginkgo-Apotheke            | Betamethasone valerate | 12L11-N01       | 1              |
| Phönix                     | Betamethasone valerate | 13091201        | 2              |
| Caelo                      | Betamethasone valerate | 13091204        | 6              |
| Caesar & Loretz GmbH, 4... | Betamethasone valerate | 13091206        | 2              |
| Alliance Health 06.02.2... | Betamethasone valerate | 13091207        | 1              |
| Caelo                      | Betamethasone valerate | 13091210        | 3              |
| Caesar & Loretz GmbH, 4... | Betamethasone valerate | 13091211        | 1              |
| Euro OTC                   | Betamethasone valerate | 13D03-N07       | 1              |
| Fagron                     | Betamethasone valerate | 13d03-n07       | 3              |
| Phönix                     | Betamethasone valerate | 13D03-N07       | 1              |
| Großhandel                 | Betamethasone valerate | 13D03-N07       | 1              |
| Caelo                      | Betamethasone valerate | 13D03-N07       | 4              |
| Fagron                     | Betamethasone valerate | 13G19-N01       | 1              |
| Fagron                     | Betamethasone valerate | 13K29B32        | 1              |
| Phonix                     | Betamethasone valerate | 13K29-B32       | 1              |
| Fagron                     | Betamethasone valerate | 14G30-B05-29617 | 1              |
| Caelo                      | Betamethasone valerate | 18121206        | 1              |
| Fagron                     | Betamethasone valerate | 20101012-1      | 1              |
| Euro OTC                   | Betamethasone valerate | 2507211181      | 1              |
| Fagron                     | Betamethasone valerate | 2B28-N01        | 1              |
| Caelo                      | Betamethasone valerate | 2x12229813      | 1              |
| Sanacorp                   | Betamethasone valerate | 30051201        | 1              |
| Caelo                      | Betamethasone valerate | 3110031         | 1              |
| Fagron                     | Betamethasone valerate | 309520          | 1              |
| Caelo                      | Betamethasone valerate | B03041205       | 1              |
| Fagron                     | Betamethasone valerate | B07-317416      | 1              |
| Fiebig 27.06.13 EK47,81    | Betamethasone valerate | B9/131          | 1              |
| Fagron                     | Betamethasone valerate | NS2072M         | 2              |
| Fagron                     | Betamethasone valerate | NS0706M         | 2              |
| Euro OTC                   | Betamethasone valerate | 1108045-02      | 3              |
| Anzag                      | Betamethasone valerate | 11K18N09        | 1              |
| Holdermann                 | Betamethasone valerate | 1208014-01      | 1              |
| Holdermann                 | Betamethasone valerate | 120801402       | 1              |
| Gehe                       | Betamethasone valerate | 1208014-04      | 1              |
| Gehe                       | Betamethasone valerate | 1311039-01      | 2              |
| Eigenherstellung           | Betamethasone valerate | 9070313         | 1              |
| Caelo                      | Betamethasone valerate | 1203403         | 1              |
| Fagron                     | Betamethasone valerate | 1208014-01      | 1              |
| Euro OTC                   | Betamethasone valerate | 120801403       | 1              |
| Caelo                      | Betamethasone valerate | 12K07-N23       | 1              |
| A.H.D.                     | Betamethasone valerate | 13D03-N07       | 1              |
| Fagron                     | Betamethasone valerate | 90616-2         | 1              |
| Caelo                      | Betamethasone valerate | 210112          | 1              |
| Euro OTC                   | Betamethasone valerate | 1008012-02      | 1              |
| PHOENIX am 05.07.2012      | Betamethasone valerate | 1008012-03      | 1              |
| Caesar & Loretz GmbH, 4... | Betamethasone valerate | 10296707        | 1              |
| Caesar & Loretz GmbH 40... | Betamethasone valerate | 10296715        | 1              |
| Kehr                       | Betamethasone valerate | 1108045-01      | 1              |
| Noweda                     | Betamethasone valerate | 1108045-01      | 1              |

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| Supplier                 | Substance              | Batch          | Spectra |
|--------------------------|------------------------|----------------|---------|
| Anzag am 24.04.2012      | Betamethasone valerate | 1108045-01     | 1       |
| Phönix Gotha             | Betamethasone valerate | 1108045-02     | 1       |
| Anzag 07.08.2012         | Betamethasone valerate | 1108045-03     | 2       |
| Euro OTC                 | Betamethasone valerate | 110804503      | 1       |
| Fagron                   | Betamethasone valerate | 11A04-N02      | 1       |
| anzag am 29.06.2012      | Betamethasone valerate | 11E18-N03      | 1       |
| Noweda                   | Betamethasone valerate | 11B21-N02      | 1       |
| Fagron                   | Betamethasone valerate | 11k18-n09      | 1       |
| Caelo                    | Betamethasone valerate | 12003402       | 1       |
| Caelo                    | Betamethasone valerate | 1208014-01     | 1       |
| Noweda                   | Betamethasone valerate | 1208014-01     | 1       |
| EuRho                    | Betamethasone valerate | 1208014-02     | 1       |
| Caelo                    | Betamethasone valerate | 1208014-03     | 1       |
| noweda                   | Betamethasone valerate | 1208014-04     | 1       |
|                          | Betamethasone valerate | 1208014-04     | 1       |
| Fiebig ek: 45,65EUR      | Betamethasone valerate | 12B28-N01      | 1       |
| Caelo                    | Betamethasone valerate | 12B28-N01      | 2       |
| FARGON                   | Betamethasone valerate | 12b28-n01      | 1       |
| agron/Krieger            | Betamethasone valerate | 12B2B-N01      | 1       |
| Großhandel               | Betamethasone valerate | 12G09-N07      | 1       |
| Caelo                    | Betamethasone valerate | 12g09-n07      | 1       |
| AHD,09.04.2013           | Betamethasone valerate | 12G09-N07      | 1       |
| FARGON                   | Betamethasone valerate | 12I11-n01      | 1       |
| Anzag                    | Betamethasone valerate | 12L11-N01      | 1       |
| Euro OTC                 | Betamethasone valerate | 12L11-N01      | 1       |
| Europ Ots Pharma         | Betamethasone valerate | 12I11-N01      | 1       |
| Caelo                    | Betamethasone valerate | 13091201       | 2       |
| Noweda                   | Betamethasone valerate | 13091203       | 2       |
| Caesar&Loretz GmbH/Anzag | Betamethasone valerate | 13091210       | 1       |
| Sanacorp                 | Betamethasone valerate | 13091210       | 1       |
| Gehe                     | Betamethasone valerate | 13091211       | 1       |
| Phönix                   | Betamethasone valerate | 13091212       | 2       |
| Alliance healthcare      | Betamethasone valerate | 13D03-N07      | 1       |
| Fagron                   | Betamethasone valerate | 13G19N01       | 1       |
| Symbiotica               | Betamethasone valerate | 14H28B01302863 | 1       |
| Euro OTC                 | Betamethasone valerate | 3313U-01181    | 1       |
| Caelo                    | Betamethasone valerate | 3110025        | 1       |
| Phönix                   | Betamethasone valerate | BV-BLT186/0512 | 1       |
| Fagron                   | Betamethasone valerate | NP1351M        | 1       |
| Fagron                   | Betamethasone valerate | NR1545M        | 1       |

- 68 355 spectra from 414 *Apo-Ident* customers from a total of 23 515 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Betamethasone valerate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Betamethasone valerate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).



|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 373           | 0              | 71 013        |
| Type B | 0              | 429           | 0              | 146 300       |
| Type C | 0              | 1260          | 18             | 68 355        |

The substance/substance group *Betamethasone valerate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.3914 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.6014 %) |
| Type C | 100.0000 % (> 99.8812 %) | 98.5915 % (> 98.3568 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20887     | 22249               | 7.47                         | 29.76                           |
| 20920     | 22861               | 5.89                         | 34.49                           |
| 21215     | 22249               | 4.17                         | 32.87                           |
| 21566     | 22249               | 7.10                         | 32.02                           |
| 21588     | 21588               | 0.00                         | 25.22                           |
| 21645     | 22249               | 5.82                         | 28.63                           |
| 21674     | 21674               | 0.00                         | 32.82                           |
| 22249     | 22249               | 0.00                         | 30.86                           |
| 22861     | 22861               | 0.00                         | 34.63                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Betamethasone, micronized**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20943-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Betamethasone, micronized; Betamethasonum, micronisatum

### Special notes

When selecting the *Betamethasone, micronized* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Betamethasone, micronized*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Betamethasone, m... | 12D26-N08        | 20943     | 40      | 1402096     |
| Fagron   | Betamethasone, m... | 13H08-N06        | 21579     | 40      | 1411037     |
| Fagron   | Betamethasone, m... | 11H31-B06-288219 | 22493     | 40      | 1608324     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Betamethasone, micronized*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 160 spectra of 5 reference samples from the substance/substance group *Betamethasone, micronized*.

| Supplier | Substance                 | Batch            | Sample ID          | Spectra |
|----------|---------------------------|------------------|--------------------|---------|
| Fagron   | Betamethasone, micronized | 11B18-N14        | 20271              | 30      |
| Fagron   | Betamethasone, micronized | 11B18-N14        | 20276              | 30      |
| Fagron   | Betamethasone, micronized | 13H08-N06        | 21579 <sup>†</sup> | 20      |
| Fagron   | Betamethasone, micronized | 14C13-B02-296165 | 22897              | 40      |
| Fagron   | Betamethasone, micronized | 15L09-B05-324091 | 22904              | 40      |

- 146 569 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 34 spectra from 22 *Apo-Ident* customers from 23 batches from the substance/substance group *Betamethasone, micronized*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                     | Substance                 | Batch            | Spectra |
|------------------------------|---------------------------|------------------|---------|
| Fagron                       | Betamethasone, micronized | 11H31-B06-288217 | 1       |
| Fagron                       | Betamethasone, micronized | 12D26-N08        | 1       |
| Fagron                       | Betamethasone, micronized | 12J01-N02        | 2       |
| Fagron                       | Betamethasone, micronized | 14C13-B02        | 2       |
| Symbiotec Pharmed Lab Ltd... | Betamethasone, micronized | 14C13-B02        | 1       |
| Fagron                       | Betamethasone, micronized | 14C13-B02-296154 | 1       |
| Fagron                       | Betamethasone, micronized | 14C13-B02-296164 | 3       |
| Fagron                       | Betamethasone, micronized | 14C13-B02-305561 | 1       |
| Fagron                       | Betamethasone, micronized | 14c13-bo2-305561 | 1       |
| BASF/Phönix                  | Betamethasone, micronized | ZBTBY13004       | 1       |
| Fagron                       | Betamethasone, micronized | 9071304          | 1       |
| Fagron                       | Betamethasone, micronized | 9K25-N13         | 1       |
| Fagron                       | Betamethasone, micronized | 11/14-N02        | 1       |
| Anzag 5.06.2012              | Betamethasone, micronized | 11K14-N02        | 1       |
| Fagron                       | Betamethasone, micronized | 9J26-N08         | 1       |
| Caelo                        | Betamethasone, micronized | 11/14-N02        | 1       |
| Caelo                        | Betamethasone, micronized | 120104/13        | 1       |
| Gehe 07.10.13                | Betamethasone, micronized | 1201-No2         | 1       |
| Fagron                       | Betamethasone, micronized | 12B20-N05        | 2       |
| Anzag 13.06.2013             | Betamethasone, micronized | 12B20-N05        | 1       |
| Noweda                       | Betamethasone, micronized | 12B20-N05        | 1       |
| Phönix                       | Betamethasone, micronized | 12B20-N05        | 1       |
| Fagron                       | Betamethasone, micronized | 12D26N08         | 1       |
| Fagron                       | Betamethasone, micronized | 12D26-N08        | 1       |
| Fiebig                       | Betamethasone, micronized | 12J01-120301-m1  | 1       |
| gehe 11.06.2013              | Betamethasone, micronized | M-X01-111201-m1  | 1       |
| Noweda                       | Betamethasone, micronized | M-X01-120301m1   | 1       |
| Unisan                       | Betamethasone, micronized | Retest09K25-N13  | 1       |
| GEHE                         | Betamethasone, micronized | 11/14-N02        | 1       |

- 69 599 spectra from 414 *Apo-Ident* customers from a total of 23 778 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Betamethasone, micronized* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Betamethasone, micronized* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 152           | 8              | 146 569       |
| <b>Type C</b> | 0              | 20            | 14             | 69 599        |

The substance/substance group *Betamethasone, micronized* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 95.0000 % (> 93.1250 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 58.8235 % (> 50.0000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20943     | 20943               | 0.00                         | 18.29                           |
| 21579     | 21579               | 0.00                         | 16.47                           |
| 22493     | 22493               | 0.00                         | 14.74                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Bifonazole**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20810-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Bifonazole; Bifonazolum

### Special notes

When selecting the *Bifonazole* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Bifonazole*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate |
|----------|------------|------------------|-----------|---------|-------------|
| Euro OTC | Bifonazole | 1206027-01       | 20810     | 40      | 1312397     |
| Fagron   | Bifonazole | 12G11-N09        | 20820     | 40      | 20120807    |
| Euro OTC | Bifonazole | 1401031-01       | 21631     | 40      | 20140220    |
| Euro OTC | Bifonazole | 1510001          | 22253     | 40      | 20151203*   |
| Caelo    | Bifonazole | 15152701         | 22906     | 40      | 20150703    |
| Caelo    | Bifonazole | 15152702         | 22907     | 40      | 20150703    |
| Fagron   | Bifonazole | 16D07-B10-324381 | 22941     | 40      | 20160419    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 280 spectra of 7 reference samples from the substance/substance group *Bifonazole*. These samples are listed above in the [calibration samples](#) section.
- 71 106 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 250 spectra of 7 reference samples from the substance/substance group *Bifonazole*.

| Supplier | Substance  | Batch      | Sample ID          | Spectra |
|----------|------------|------------|--------------------|---------|
| Fagron   | Bifonazole | 11A13-N13  | 20274              | 30      |
| Euro OTC | Bifonazole | 1401031-01 | 21631 <sup>†</sup> | 20      |
| Euro OTC | Bifonazole | 1510001    | 22253 <sup>†</sup> | 20      |
| Caelo    | Bifonazole | 15152702   | 22955              | 40      |
| Caelo    | Bifonazole | 151527     | 23364              | 40      |
| Euro OTC | Bifonazole | 1703041    | 23395              | 40      |
| Euro OTC | Bifonazole | 1510001    | 22253SI            | 60      |

- 146 479 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 33 spectra from 18 *Apo-Ident* customers from 21 batches from the substance/substance group *Bifonazole*.

| Supplier | Substance  | Batch            | Spectra |
|----------|------------|------------------|---------|
| Fagron   | Bifonazole | 11F20-N06        | 1       |
| Euro OTC | Bifonazole | 1206027-01       | 2       |
| Fagron   | Bifonazole | 11071202         | 1       |
| Euro OTC | Bifonazole | 1206027-02       | 1       |
| Fagron   | Bifonazole | 12E29-N03        | 3       |
| Fagron   | Bifonazole | 12G11-N09        | 2       |
| Euro OTC | Bifonazole | 13G10N02         | 1       |
| Fagron   | Bifonazole | 13G10-N02        | 1       |
| Fagron   | Bifonazole | 14C28-B03-292388 | 1       |
| Fagron   | Bifonazole | 14K10-B01-300541 | 4       |
| Fagron   | Bifonazole | 14K10-B01-306783 | 3       |
| Fagron   | Bifonazole | 14K10-B01-308349 | 1       |
| Fagron   | Bifonazole | 14K10-B01-312067 | 1       |
| Fagron   | Bifonazole | 14K10-B01-316618 | 1       |
| Euro OTC | Bifonazole | 1510001-02       | 3       |
| Caelo    | Bifonazole | 15152701         | 2       |
| Gehe     | Bifonazole | 15152703         | 1       |
| Fagron   | Bifonazole | 16D07-B10-321576 | 1       |
| Fagron   | Bifonazole | 16D07-B10-324380 | 1       |
| Fagron   | Bifonazole | 16D07-B10-32480  | 1       |
| Fargon   | Bifonazole | 14k10-b01-300541 | 1       |

- 69 600 spectra from 414 *Apo-Ident* customers from a total of 23 781 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Bifonazole* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Bifonazole* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 280           | 0              | 71 106        |
| <b>Type B</b> | 0              | 250           | 0              | 146 479       |
| <b>Type C</b> | 0              | 33            | 0              | 69 600        |

The substance/substance group *Bifonazole* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.8571 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.6000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 81.8182 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20810     | 20810               | 0.00                         | 36.15                           |
| 20820     | 22253               | 7.68                         | 33.99                           |
| 21631     | 22253               | 2.67                         | 40.34                           |
| 22253     | 22253               | 0.00                         | 38.38                           |
| 22906     | 22253               | 5.20                         | 37.03                           |
| 22907     | 22253               | 6.32                         | 36.51                           |
| 22941     | 22253               | 5.44                         | 36.21                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Biotin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20414-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Biotin; Biotinum

### Special notes

When selecting the *Biotin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Biotin*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Fagron   | Biotin    | 13K29-N02  | 21221     | 40      | 20131204    |
| Euro OTC | Biotin    | 1402028-01 | 21632     | 40      | 20140404    |
| Euro OTC | Biotin    | 1508030    | 21904     | 40      | 20150925*   |
| Euro OTC | Biotin    | 1610003    | 22855     | 40      | 20161110*   |
| Caelo    | Biotin    | 16164313   | 22902     | 40      | 20160216    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Biotin*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 7 reference samples from the substance/substance group *Biotin*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Fagron   | Biotin    | 10I17-N08  | 20414              | 40      |
| Euro OTC | Biotin    | 1402028-01 | 21632 <sup>†</sup> | 20      |
| Euro OTC | Biotin    | 1508030    | 21904 <sup>†</sup> | 20      |
| Euro OTC | Biotin    | 1603017    | 22507              | 40      |
| Caelo    | Biotin    | 16164313   | 22901              | 40      |
| Caelo    | Biotin    | 163432     | 23029              | 40      |
| Caelo    | Biotin    | 163432     | 23063              | 40      |

- 146 489 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 33 spectra from 16 *Apo-Ident* customers from 21 batches from the substance/substance group *Biotin*.

| Supplier | Substance | Batch            | Spectra |
|----------|-----------|------------------|---------|
| Euro OTC | Biotin    | 2041517          | 1       |
| Euro OTC | Biotin    | 3021501          | 1       |
| EuRho    | Biotin    | 111039-01        | 1       |
| Euro OTC | Biotin    | 1111039-02       | 2       |
| Euro OTC | Biotin    | 1111039-03       | 1       |
| Fagron   | Biotin    | 12111302         | 1       |
| Caelo    | Biotin    | 12A23-N03        | 1       |
| Fagron   | Biotin    | 12A23-N03        | 1       |
| Fagron   | Biotin    | 12C14-N01        | 2       |
| Euro OTC | Biotin    | 1301026-01       | 3       |
| Fagron   | Biotin    | 13K29-N02        | 3       |
| Euro OTC | Biotin    | 1402028-01       | 3       |
| Caelo    | Biotin    | 1402028-01       | 2       |
| Euro OTC | Biotin    | 1411047-01       | 2       |
| Fagron   | Biotin    | 14d04-b07-292963 | 1       |
| Euro OTC | Biotin    | 1610003-01       | 1       |
| Euro OTC | Biotin    | 1610003-02       | 1       |
| Euro OTC | Biotin    | 28071506         | 1       |
| Fagron   | Biotin    | 1017-N08         | 1       |
| Euro OTC | Biotin    | 1111039-01       | 1       |
| Fagron   | Biotin    | 13081203         | 1       |
| Fagron   | Biotin    | 13111202         | 1       |
| Fagron   | Biotin    | 20110634         | 1       |

- 69 600 spectra from 414 *Apo-Ident* customers from a total of 23 780 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Biotin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Biotin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 240           | 0              | 146 489       |
| <b>Type C</b> | 0              | 33            | 0              | 69 600        |

The substance/substance group *Biotin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 81.8182 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21221     | 21904               | 7.22                         | 73.67                           |
| 21632     | 21904               | 3.09                         | 69.65                           |
| 21904     | 21904               | 0.00                         | 71.21                           |
| 22855     | 22855               | 0.00                         | 70.34                           |
| 22902     | 21904               | 4.39                         | 69.48                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Bismuth gallath, basic**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21252-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Bismuth gallath, basic; Bismuthi subgallas; Bismutum subgallicum

### Special notes

When selecting the *Bismuth gallath, basic* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Bismuth gallath, basic*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Caelo    | Bismuth gallath,... | 13179105         | 21252     | 40      | 1412254     |
| Fagron   | Bismuth gallath,... | 15B02-B04-309481 | 22597     | 40      | 20150226    |
| Caelo    | Bismuth gallath,... | 17004102         | 23372     | 40      | 20170214    |
| Fagron   | Bismuth gallath,... | 16K17-B04-335597 | 23570     | 40      | 20170623    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Bismuth gallath, basic*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 4 reference samples from the substance/substance group *Bismuth gallath, basic*.

| Supplier    | Substance              | Batch            | Sample ID | Spectra |
|-------------|------------------------|------------------|-----------|---------|
| zu erfassen | Bismuth gallath, basic | pending          | 20466     | 40      |
| Caelo       | Bismuth gallath, basic | 13179105         | 21553     | 60      |
| Fagron      | Bismuth gallath, basic | 15J26-B02-317883 | 22598     | 40      |
| Caelo       | Bismuth gallath, basic | 170041           | 23359     | 40      |

- 146 549 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 211 spectra from 115 *Apo-Ident* customers from 100 batches from the substance/substance group *Bismuth gallath, basic*.

| Supplier               | Substance              | Batch    | Spectra |
|------------------------|------------------------|----------|---------|
| siehe WE-Prüfprotokoll | Bismuth gallath, basic | 4/09     | 1       |
| Caelo                  | Bismuth gallath, basic | 12172402 | 4       |

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| <b>Supplier</b> | <b>Substance</b>       | <b>Batch</b>      | <b>Spectra</b> |
|-----------------|------------------------|-------------------|----------------|
| Caelo           | Bismuth gallath, basic | 12172409          | 6              |
| Caelo           | Bismuth gallath, basic | 12172412          | 1              |
| Fagron          | Bismuth gallath, basic | 12B02-B04-304408  | 1              |
| Fagron          | Bismuth gallath, basic | 12C13-N03         | 4              |
| sanacorp        | Bismuth gallath, basic | 13/1818B13-292057 | 1              |
| Fagron          | Bismuth gallath, basic | 13/18-B13294098   | 1              |
| Caelo           | Bismuth gallath, basic | 13/18-B13-292057  | 1              |
| Fagron          | Bismuth gallath, basic | 13/18-B-13-292057 | 1              |
| Fagron          | Bismuth gallath, basic | 13/18-B13-292058  | 2              |
| Bombastus       | Bismuth gallath, basic | 13/18-B13-292058  | 1              |
| Caelo           | Bismuth gallath, basic | 13/18-B13-292058  | 1              |
| Fagron          | Bismuth gallath, basic | 13/18-B13-294108  | 2              |
| Caelo           | Bismuth gallath, basic | 13179101          | 1              |
| Fagron          | Bismuth gallath, basic | 13/18-B13-294098  | 1              |
| Caelo           | Bismuth gallath, basic | 13179105          | 1              |
| Fagron          | Bismuth gallath, basic | 13179111          | 1              |
| Caelo           | Bismuth gallath, basic | 13179111          | 7              |
| Fagron          | Bismuth gallath, basic | 1318-B13-292057   | 1              |
| Fagron          | Bismuth gallath, basic | 1318-b13-292058   | 1              |
| Fagron          | Bismuth gallath, basic | 1318b13292058     | 1              |
| Fagron          | Bismuth gallath, basic |                   | 1              |
| Fagron          | Bismuth gallath, basic | 1318B13294108     | 1              |
| Fagron          | Bismuth gallath, basic | 13G10-N12         | 4              |
| ahd/lamotte     | Bismuth gallath, basic | 13718b13292058    | 1              |
| Fagron          | Bismuth gallath, basic | 13I18-B13         | 5              |
| Fagron          | Bismuth gallath, basic | 13I18-b13-292057  | 1              |
| Fagron          | Bismuth gallath, basic | 13I18-B13-292057  | 1              |
| Fagron          | Bismuth gallath, basic | 13I18-B13-294098  | 4              |
| Fagron          | Bismuth gallath, basic | 13I18-B13-294108  | 5              |
| Caelo           | Bismuth gallath, basic | 13I18-B13-294108  | 1              |
| Fagron          | Bismuth gallath, basic | 13K08-N03         | 3              |
| Caelo           | Bismuth gallath, basic | 14224103          | 3              |
| Infectopharm    | Bismuth gallath, basic | 14224103          | 1              |
| Fagron          | Bismuth gallath, basic | 14H13-B07-303639  | 3              |
| Fagron          | Bismuth gallath, basic | 14H13B07303639    | 1              |
| Fagron          | Bismuth gallath, basic | 15/26-B02-320473  | 1              |
| Caelo           | Bismuth gallath, basic | 15080602          | 2              |
| Alliance H.     | Bismuth gallath, basic | 15080602          | 1              |
| Caelo           | Bismuth gallath, basic | 15080603          | 1              |
| Caelo           | Bismuth gallath, basic | 15080606          | 4              |
| Caelo           | Bismuth gallath, basic | 15200904          | 2              |
| Caelo           | Bismuth gallath, basic | 15200905          | 1              |
| Caelo           | Bismuth gallath, basic | 1520910           | 1              |
| Caelo           | Bismuth gallath, basic | 1520913           | 1              |
| Caelo           | Bismuth gallath, basic | 15B02B04304413    | 1              |
| Fagron          | Bismuth gallath, basic | 15B02-B04         | 1              |
| Fagron          | Bismuth gallath, basic | 15B02-B04-209481  | 1              |
| Fagron          | Bismuth gallath, basic | 15B02-B04-304408  | 4              |
| Caelo           | Bismuth gallath, basic | 15B02-B04-304408  | 3              |
| Caelo           | Bismuth gallath, basic | 15B02-B04-309481  | 1              |
| Fagron          | Bismuth gallath, basic | 15B02-B04-304413  | 2              |
| Fagron          | Bismuth gallath, basic | 15B02-B04-309481  | 4              |
| Fagron          | Bismuth gallath, basic | 15b02-B04-309481  | 1              |
| Fargon/ Noweda  | Bismuth gallath, basic | 15B02-B04-309481  | 1              |
| Fagron          | Bismuth gallath, basic | 15B02-B04-311878  | 1              |
| Fagron          | Bismuth gallath, basic | 15C27-B02-311879  | 1              |
| Fagron          | Bismuth gallath, basic | 15H05-B07         | 1              |
| Fagron          | Bismuth gallath, basic | 15H05-B07-311880  | 2              |
| Caelo           | Bismuth gallath, basic | 15J26B02-321313   | 1              |
| Fagron          | Bismuth gallath, basic | 15J26-B02-317883  | 5              |

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| Supplier                   | Substance              | Batch            | Spectra |
|----------------------------|------------------------|------------------|---------|
| Fagron                     | Bismuth gallath, basic | 15J26-B022       | 1       |
| Fagron                     | Bismuth gallath, basic | 15J26-B02-320473 | 2       |
| Fagron                     | Bismuth gallath, basic | 15J26-B02-321313 | 3       |
| Caelo                      | Bismuth gallath, basic | 16038308         | 4       |
| Caesar & Loretz GmbH Hi... | Bismuth gallath, basic | 16038308         | 1       |
| Caelo                      | Bismuth gallath, basic | 16038310         | 3       |
| Caelo                      | Bismuth gallath, basic | 17004102         | 1       |
| Fagron                     | Bismuth gallath, basic | 2012006724       | 2       |
| Fagron                     | Bismuth gallath, basic | 2014006082       | 1       |
| Fagron                     | Bismuth gallath, basic | 2015007568       | 1       |
| Caelo                      | Bismuth gallath, basic | 23121410         | 1       |
| Caelo                      | Bismuth gallath, basic | 2414E-01185      | 1       |
| Fagron                     | Bismuth gallath, basic | 5121             | 1       |
| Caelo                      | Bismuth gallath, basic | 81297468         | 5       |
| Caelo                      | Bismuth gallath, basic | 9205701          | 1       |
| Caelo                      | Bismuth gallath, basic | 9205703          | 1       |
| Phoenix, Jembke            | Bismuth gallath, basic | 10135101         | 1       |
| Fagron                     | Bismuth gallath, basic | 10H31-N01        | 1       |
| Caelo                      | Bismuth gallath, basic | 10D23-N05        | 1       |
| Caelo                      | Bismuth gallath, basic | 11127203         | 1       |
| Caelo                      | Bismuth gallath, basic | 1127203          | 1       |
| Fagron                     | Bismuth gallath, basic | 11F15-N03        | 1       |
| Fagron                     | Bismuth gallath, basic | 12/13-N11        | 1       |
| Sanacorp                   | Bismuth gallath, basic | 12/13-N11        | 1       |
| Phönix                     | Bismuth gallath, basic | 12-13-N11        | 1       |
| Caelo                      | Bismuth gallath, basic | 12166901         | 2       |
| Caelo                      | Bismuth gallath, basic | 1217240          | 1       |
| Caelo                      | Bismuth gallath, basic | 12172401         | 1       |
| Gehe                       | Bismuth gallath, basic | 12172401         | 1       |
| Alliance                   | Bismuth gallath, basic | 12172402         | 1       |
| Caelo                      | Bismuth gallath, basic | 12c13-n03        | 1       |
| Anzag                      | Bismuth gallath, basic | 12e16-n03        | 1       |
| Caelo                      | Bismuth gallath, basic | 12c13-no3        | 1       |
| Fagron                     | Bismuth gallath, basic | 12E16-N03        | 1       |
| Klenk                      | Bismuth gallath, basic | 12E16-N03        | 1       |
| Caelo                      | Bismuth gallath, basic | 12E16-N03        | 1       |
| Phönix                     | Bismuth gallath, basic | 12E16-N03        | 1       |
| Fagron                     | Bismuth gallath, basic | 12E16-N03        | 1       |
| Fagron                     | Bismuth gallath, basic | 12K26-N01        | 4       |
| Fagron                     | Bismuth gallath, basic | 13D19-N02        | 5       |
| Sanacorp                   | Bismuth gallath, basic | 13D19-N02        | 1       |
| Apomix/Noweda              | Bismuth gallath, basic | 13D19-N02        | 1       |
| Caelo                      | Bismuth gallath, basic | 13D19-N02        | 2       |
| Alliance Healthcare        | Bismuth gallath, basic | 13D19-N02        | 2       |
| Fargron                    | Bismuth gallath, basic | 13D19-N02        | 1       |
| Fagron                     | Bismuth gallath, basic | 13E21-N03        | 2       |
| Fagron                     | Bismuth gallath, basic | 2010002685       | 2       |
| Fagron                     | Bismuth gallath, basic | 2012000059       | 3       |
| Anzag                      | Bismuth gallath, basic | 2012000059       | 2       |
| PHOENIX am 17.01.2014      | Bismuth gallath, basic | 2012006724       | 1       |
| Fagron                     | Bismuth gallath, basic | 2015005560       | 1       |
| Fagron                     | Bismuth gallath, basic | 411092-3-P       | 1       |
| Caelo                      | Bismuth gallath, basic | 5208I-01185      | 1       |
| Caelo                      | Bismuth gallath, basic | 8129768          | 1       |
| Caelo                      | Bismuth gallath, basic | 92057409         | 1       |
| Caelo                      | Bismuth gallath, basic | B-150513-1       | 1       |
| Fargron                    | Bismuth gallath, basic | 13/18-B13-294108 | 1       |
| Fagron                     | Bismuth gallath, basic | 14H13-B07        | 1       |
| Martinus Apotheke          | Bismuth gallath, basic | keine            | 1       |
| Caelo                      | Bismuth gallath, basic | 12C13-N03        | 1       |

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| Supplier | Substance              | Batch            | Spectra |
|----------|------------------------|------------------|---------|
| Caelo    | Bismuth gallath, basic | 12I13-N11        | 1       |
| Fagron   | Bismuth gallath, basic | 13I18-B13-292058 | 1       |
| Fagron   | Bismuth gallath, basic | 13i18-b13-294108 | 1       |

- 69 422 spectra from 414 *Apo-Ident* customers from a total of 23 702 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Bismuth gallath, basic* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Bismuth gallath, basic* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 154           | 6              | 71 226        |
| <b>Type B</b> | 0              | 104           | 76             | 146 549       |
| <b>Type C</b> | 0              | 187           | 24             | 69 422        |

The substance/substance group *Bismuth gallath, basic* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate        |
|---------------|--------------------------|-------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 96.2500 % (> 94.3750 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 57.7778 % (> 56.1111 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 88.6256 % (> 87.2038 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21252     | 21252               | 0.00                         | 140.58                          |
| 22597     | 21252               | 9.82                         | 141.21                          |
| 23372     | 21252               | 3.18                         | 143.09                          |
| 23570     | 21252               | 3.03                         | 139.31                          |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Boric acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20182-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Boric acid; Acidum boricum

### Special notes

When selecting the *Boric acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Boric acid*:

| Supplier | Substance  | Batch     | Sample ID | Spectra | Certificate |
|----------|------------|-----------|-----------|---------|-------------|
| Fagron   | Boric acid | 13I04-N06 | 21228     | 40      | 20130920    |
| Caelo    | Boric acid | 14133119  | 21804     | 40      | 20140509    |
| Caelo    | Boric acid | 15425112  | 22964     | 40      | 20160104    |
| Caelo    | Boric acid | 170613    | 23286     | 40      | 20170316*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Boric acid*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 110 spectra of 3 reference samples from the substance/substance group *Boric acid*.

| Supplier | Substance  | Batch    | Sample ID          | Spectra |
|----------|------------|----------|--------------------|---------|
| Fagron   | Boric acid | 9L21-N08 | 20182              | 50      |
| Caelo    | Boric acid | 14133119 | 21804 <sup>†</sup> | 20      |
| Caelo    | Boric acid | 15242903 | 22965              | 40      |

- 146 619 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 28 spectra from 19 *Apo-Ident* customers from 25 batches from the substance/substance group *Boric acid*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier    | Substance  | Batch            | Spectra |
|-------------|------------|------------------|---------|
| Caelo       | Boric acid | 9324021          | 1       |
| Caelo       | Boric acid | 2808A-01019      | 1       |
| Fagron      | Boric acid | 13I04-N06        | 3       |
| Caelo       | Boric acid | 14133119         | 1       |
| Caelo       | Boric acid | 15095103         | 2       |
| Caelo       | Boric acid | 812Q-01018       | 1       |
| Sanacorp    | Boric acid | 1/AKD3           | 1       |
| Caelo       | Boric acid | 10227913         | 1       |
| Caelo       | Boric acid | 11D13-N08        | 1       |
| Caelo       | Boric acid | 12260537         | 1       |
| Caelo       | Boric acid | 14095202         | 1       |
| Fagron      | Boric acid | 14133101         | 1       |
| Caelo       | Boric acid | 14133113         | 1       |
| Fagron      | Boric acid | 14B07-B02-295752 | 1       |
| Caelo       | Boric acid | 15425101         | 1       |
| Caelo       | Boric acid | 9324036          | 1       |
| Caelo       | Boric acid | 9324043          | 1       |
| Fagron      | Boric acid | 11d13-n08        | 1       |
| Caelo       | Boric acid | 12238901         | 1       |
| Nachprüfung | Boric acid |                  | 1       |
| Caelo       | Boric acid | 12260502         | 1       |
| Caelo       | Boric acid | 12260507         | 1       |
| Caelo       | Boric acid | 1234             | 1       |
| Caelo       | Boric acid | 12260519         | 1       |
| Fagron      | Boric acid | 12f01-n08        | 1       |

- 69 605 spectra from 414 *Apo-Ident* customers from a total of 23 778 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Boric acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Boric acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 110           | 0              | 146 619       |
| <b>Type C</b> | 0              | 28            | 0              | 69 605        |

The substance/substance group *Boric acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.5455 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 78.5714 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several

new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21228     | 23286               | 12.21                        | 51.97                           |
| 21804     | 23286               | 15.39                        | 51.90                           |
| 22964     | 23286               | 7.12                         | 51.73                           |
| 23286     | 23286               | 0.00                         | 51.60                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Budesonide, micronized**  
 Substance class APIs & excipients, solid  
 Report date 19/01/2018  
 Report number 20569-2018-01-19  
 Executing company HiperScan GmbH  
 Weißeritzstraße 3  
 01067 Dresden  
 Germany

### Relevant substance names

Budesonide, micronized; Budesonidum micronisatum

### Special notes

When selecting the *Budesonide, micronized* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
 Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
 AA004 *Erstellung und Validierung eines IdentModul-Updates*  
 Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Budesonide, micronized*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------|-----------|---------|--------------------|
| Caelo    | Budesonide, micr... | 11351704   | 20808     | 30      | AR-15-FG-005286-01 |
| Euro OTC | Budesonide, micr... | 1311022-01 | 21620     | 40      | 20140113           |
| Euro OTC | Budesonide, micr... | 1604018    | 22537     | 40      | 20160509*          |
| Caelo    | Budesonide, micr... | 161431     | 22627     | 40      | 20160606*          |
| Caelo    | Budesonide, micr... | 15344004   | 22649     | 40      | 20151116           |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Budesonide, micr... | 16J04-B01-326581 | 22888     | 40      | 20161026    |
| Euro OTC | Budesonide, micr... | 1311022-01       | 21620SI   | 25      | 20140113    |
| Euro OTC | Budesonide, micr... | 1604018          | 22537SI   | 23      | 20160509*   |
| Caelo    | Budesonide, micr... | 161431           | 22627SI   | 25      | 20160606*   |
| Caelo    | Budesonide, micr... | 15344004         | 22649SI   | 30      | 20151116    |
| Fagron   | Budesonide, micr... | 16J04-B01-326581 | 22888SI   | 30      | 20161026    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 363 spectra of 11 reference samples from the substance/substance group *Budesonide, micronized*. These samples are listed above in the [calibration samples](#) section.
- 71 023 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 236 spectra of 8 reference samples from the substance/substance group *Budesonide, micronized*.

| Supplier | Substance              | Batch            | Sample ID            | Spectra |
|----------|------------------------|------------------|----------------------|---------|
| Caelo    | Budesonide, micronized | 11351706         | 20569                | 40      |
| Caelo    | Budesonide, micronized | 11351706         | 20800                | 40      |
| Euro OTC | Budesonide, micronized | 1311022-01       | 21620 <sup>†</sup>   | 20      |
| Fagron   | Budesonide, micronized | 16J04-B01-326581 | 22841                | 40      |
| Caelo    | Budesonide, micronized | 170788           | 23279                | 40      |
| Euro OTC | Budesonide, micronized | 1311022-01       | 21620SI <sup>†</sup> | 12      |
| Fagron   | Budesonide, micronized | 16J04-B01-326581 | 22841SI              | 24      |
| Caelo    | Budesonide, micronized | 170788           | 23279SI              | 20      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 493 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 113 spectra from 45 *Apo-Ident* customers from 58 batches from the substance/substance group *Budesonide, micronized*.

| Supplier  | Substance              | Batch            | Spectra |
|-----------|------------------------|------------------|---------|
| Caelo     | Budesonide, micronized | 12295105         | 1       |
| Caelo     | Budesonide, micronized | 12295106         | 2       |
| Caelo     | Budesonide, micronized | 12295108         | 1       |
| Caelo     | Budesonide, micronized | 12295109         | 3       |
| Caelo     | Budesonide, micronized | 12295110         | 3       |
| Caelo     | Budesonide, micronized | 12295111         | 5       |
| Caelo     | Budesonide, micronized | 1305004-01       | 2       |
| Euro OTC  | Budesonide, micronized | 1311022-01       | 3       |
| Fagron    | Budesonide, micronized | 13A07-N09        | 2       |
| Fagron    | Budesonide, micronized | 13H22-N03        | 3       |
| Caelo     | Budesonide, micronized | 140711707        | 1       |
| Caelo     | Budesonide, micronized | 14071701         | 1       |
| sanacorp  | Budesonide, micronized | 14071701         | 1       |
| Caelo     | Budesonide, micronized | 14071702         | 6       |
| Caelo     | Budesonide, micronized | 14071706         | 1       |
| Caelo     | Budesonide, micronized | 14071707         | 2       |
| Caelo     | Budesonide, micronized | 14071713         | 1       |
| Caelo     | Budesonide, micronized | 14071714         | 4       |
| Caelo     | Budesonide, micronized | 14071716         | 2       |
| Caelo     | Budesonide, micronized | 14071717         | 3       |
| Caelo     | Budesonide, micronized | 1471707          | 1       |
| Fagron    | Budesonide, micronized | 14A30-B09291366  | 1       |
| Fagron    | Budesonide, micronized | 14A30-B09-291366 | 2       |
| Fagron    | Budesonide, micronized | 14H15-B02        | 3       |
| Fagron    | Budesonide, micronized | 14H15-B02-297925 | 1       |
| Fagron    | Budesonide, micronized | 14H15-B02-297926 | 1       |
| Fagron    | Budesonide, micronized | 14H15-B02-301972 | 1       |
| Caelo     | Budesonide, micronized | 15173802         | 1       |
| Caelo     | Budesonide, micronized | 15173803         | 5       |
| Fagron    | Budesonide, micronized | 14H15-B02-301971 | 1       |
| Caelo     | Budesonide, micronized | 15173806         | 1       |
| Caelo     | Budesonide, micronized | 15173810         | 2       |
| Caelo     | Budesonide, micronized | 15173811         | 4       |
| Caelo     | Budesonide, micronized | 15173812         | 1       |
| Caelo     | Budesonide, micronized | 15344003         | 5       |
| Caelo     | Budesonide, micronized | 15344008         | 2       |
| Caelo     | Budesonide, micronized | 15344010         | 2       |
| Caelo     | Budesonide, micronized | 15344012         | 2       |
| Fagron    | Budesonide, micronized | 15E27B10         | 1       |
| Fagron    | Budesonide, micronized | 15E27-B10-308321 | 1       |
| Fagron    | Budesonide, micronized | 15E27-B10-308322 | 1       |
| Fagron    | Budesonide, micronized | 15E27-B10-315704 | 1       |
| Caelo     | Budesonide, micronized | 16143102         | 1       |
| Bombastus | Budesonide, micronized | 21100M1A0021321  | 1       |
| Fagron    | Budesonide, micronized | 21100M1B0011621  | 1       |

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| Supplier                | Substance              | Batch       | Spectra |
|-------------------------|------------------------|-------------|---------|
| Fagron                  | Budesonide, micronized | 2184        | 1       |
| Caelo                   | Budesonide, micronized | ChB14071717 | 1       |
| Caelo                   | Budesonide, micronized | 11175014    | 2       |
| Caelo                   | Budesonide, micronized | 11175015    | 1       |
| Caelo                   | Budesonide, micronized | 11351701    | 1       |
| Caelo                   | Budesonide, micronized | 11351706    | 5       |
| Caelo                   | Budesonide, micronized | 11351707    | 3       |
| Caelo                   | Budesonide, micronized | 11351713    | 1       |
| Caelo                   | Budesonide, micronized | 12295103    | 1       |
| Fagron                  | Budesonide, micronized | 12G23-N01   | 2       |
| Fagron                  | Budesonide, micronized | 12J29-N05   | 1       |
| Caelo                   | Budesonide, micronized | 21100M1     | 1       |
| VDI 23.10.14 19,50 euro | Budesonide, micronized | 14071707    | 1       |
| Caelo                   | Budesonide, micronized | 11351703    | 1       |
| Sanacorp,               | Budesonide, micronized | 16143103    | 1       |

- 69 520 spectra from 414 *Apo-Ident* customers from a total of 23 743 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Budesonide, micronized* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Budesonide, micronized* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 363           | 0              | 71 023        |
| <b>Type B</b> | 0              | 236           | 0              | 146 493       |
| <b>Type C</b> | 0              | 113           | 0              | 69 520        |

The substance/substance group *Budesonide, micronized* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.3471 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.4576 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 94.6903 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20808     | 20808               | 0.00                         | 36.70                           |
| 21620     | 20808               | 6.29                         | 34.61                           |
| 22537     | 22537               | 0.00                         | 28.39                           |
| 22627     | 22627               | 0.00                         | 35.72                           |
| 22649     | 20808               | 6.75                         | 34.18                           |
| 22888     | 22627               | 5.95                         | 33.40                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Butylated hydroxytoluene**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21307-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Butylated hydroxytoluene; Butylhydroxytoluenum; Butylhydroxytoluolum

### Special notes

When selecting the *Butylated hydroxytoluene* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Butylated hydroxytoluene*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate        |
|----------|---------------------|----------|-----------|---------|--------------------|
| Caelo    | Butylated hydrox... | 13354602 | 21307     | 40      | 20131105           |
| Caelo    | Butylated hydrox... | 13354604 | 21355     | 40      | AR-15-FG-007846-02 |
| Caelo    | Butylated hydrox... | 15172103 | 22350     | 40      | 20150529           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Butylated hydroxytoluene*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 5 reference samples from the substance/substance group *Butylated hydroxytoluene*.

| Supplier | Substance                | Batch    | Sample ID          | Spectra |
|----------|--------------------------|----------|--------------------|---------|
| Caelo    | Butylated hydroxytoluene | 11131002 | 20282              | 40      |
| Caelo    | Butylated hydroxytoluene | 15172103 | 21911              | 60      |
| Caelo    | Butylated hydroxytoluene | 15172103 | 22281              | 60      |
| Caelo    | Butylated hydroxytoluene | 15172103 | 22350 <sup>†</sup> | 20      |
| Caelo    | Butylated hydroxytoluene | 163163   | 23356              | 40      |

- 146 509 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 159 spectra from 112 *Apo-Ident* customers from 40 batches from the substance/substance group *Butylated hydroxytoluene*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier                     | Substance                | Batch      | Spectra |
|------------------------------|--------------------------|------------|---------|
| Caelo                        | Butylated hydroxytoluene | 2170717    | 1       |
| Caelo                        | Butylated hydroxytoluene | 7031403    | 1       |
| Caelo                        | Butylated hydroxytoluene | 716M-02851 | 1       |
| Caelo                        | Butylated hydroxytoluene | 12280206   | 5       |
| Caelo                        | Butylated hydroxytoluene | 12382309   | 7       |
| Caelo                        | Butylated hydroxytoluene | 13354602   | 6       |
| Caelo                        | Butylated hydroxytoluene | 13354604   | 5       |
| Gehe                         | Butylated hydroxytoluene | 13354604   | 1       |
| Th. Geyer                    | Butylated hydroxytoluene | 13354604   | 2       |
| Bombastus                    | Butylated hydroxytoluene | 13354604   | 1       |
| Caelo                        | Butylated hydroxytoluene | 13354609   | 3       |
| Phoenix                      | Butylated hydroxytoluene | 13354609   | 1       |
| Caelo                        | Butylated hydroxytoluene | 13354611   | 3       |
| Caelo                        | Butylated hydroxytoluene | 1400501    | 1       |
| Caelo                        | Butylated hydroxytoluene | 143004502  | 1       |
| Caelo                        | Butylated hydroxytoluene | 14300501   | 6       |
| Caelo                        | Butylated hydroxytoluene | 14300502   | 5       |
| Caelo                        | Butylated hydroxytoluene | 14300505   | 5       |
| Sanacorp                     | Butylated hydroxytoluene | 14300505   | 1       |
| Caelo                        | Butylated hydroxytoluene | 14300506   | 1       |
| Caelo                        | Butylated hydroxytoluene | 15094501   | 6       |
| Caelo                        | Butylated hydroxytoluene | 15172101   | 8       |
| Caelo                        | Butylated hydroxytoluene | 15172103   | 14      |
| Noweda                       | Butylated hydroxytoluene | 15172103   | 1       |
| Caesar & Loretz GmbH Hi. . . | Butylated hydroxytoluene | 15172103   | 1       |
| Caelo                        | Butylated hydroxytoluene | 15172105   | 8       |
| Fagron                       | Butylated hydroxytoluene | 15426801   | 1       |
| Phoenix                      | Butylated hydroxytoluene | 15426801   | 1       |
| Caelo                        | Butylated hydroxytoluene | 15426801   | 1       |
| Celo                         | Butylated hydroxytoluene | 15426801   | 1       |
| Caelo                        | Butylated hydroxytoluene | 15426807   | 3       |
| Caesar & Loretz              | Butylated hydroxytoluene | 15426801   | 1       |
| Gehe                         | Butylated hydroxytoluene | 15426807   | 1       |
| Caelo                        | Butylated hydroxytoluene | 16316301   | 2       |
| Caelo                        | Butylated hydroxytoluene | 122080206  | 1       |
| Caelo                        | Butylated hydroxytoluene | 12280201   | 2       |
| Phoenix                      | Butylated hydroxytoluene | 3111201    | 1       |
| Caelo                        | Butylated hydroxytoluene | 11131006   | 2       |
| Fagron                       | Butylated hydroxytoluene | 11308701   | 1       |
| Noweda                       | Butylated hydroxytoluene | 12158201   | 1       |
| Caelo                        | Butylated hydroxytoluene | 12158201   | 3       |
| Caelo                        | Butylated hydroxytoluene | 12158204   | 5       |
| Anzag 24.10.12               | Butylated hydroxytoluene | 12207004   | 1       |
| Caelo                        | Butylated hydroxytoluene | 12207005   | 4       |
| Caelo                        | Butylated hydroxytoluene | 1220705    | 1       |
| Caelo                        | Butylated hydroxytoluene | 12280203   | 8       |
| Großhandel                   | Butylated hydroxytoluene | 12280206   | 1       |
| Anzag 122.04.13 ek: 3,76EUR  | Butylated hydroxytoluene | 12280206   | 1       |
| Caelo                        | Butylated hydroxytoluene | 12382302   | 6       |
| Caelo                        | Butylated hydroxytoluene | 12382304   | 7       |
| Noweda                       | Butylated hydroxytoluene | 12382304   | 1       |
| Phoenix                      | Butylated hydroxytoluene | 12382305   | 1       |
| Caelo                        | Butylated hydroxytoluene | 12382307   | 3       |
| Caelo                        | Butylated hydroxytoluene | 12382312   | 1       |
| Caelo                        | Butylated hydroxytoluene | 20161112-1 | 1       |
| Caelo                        | Butylated hydroxytoluene | 2113U02851 | 1       |

- 69 474 spectra from 414 *Apo-Ident* customers from a total of 23 761 batches from a further 696

substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Butylated hydroxytoluene* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Butylated hydroxytoluene* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 120           | 0              | 71 266        |
| Type B | 0              | 220           | 0              | 146 509       |
| Type C | 0              | 152           | 7              | 69 474        |

The substance/substance group *Butylated hydroxytoluene* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.2727 %) |
| Type C | 100.0000 % (> 99.8813 %) | 95.5975 % (> 93.7107 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21307     | 21355               | 4.27                         | 72.41                           |
| 21355     | 21355               | 0.00                         | 72.74                           |
| 22350     | 21355               | 1.13                         | 70.60                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Caffeine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20962-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Caffeine; Coffeinum

### Special notes

When selecting the *Caffeine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Caffeine*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Euro OTC | Caffeine  | 1211012-01 | 20962     | 40      | 1412248     |
| Caelo    | Caffeine  | 12317911   | 21205     | 40      | 20121113    |
| Caelo    | Caffeine  | 13233105   | 21456     | 40      | 20131008    |
| Caelo    | Caffeine  | 13233104   | 21548     | 40      | 20131008    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Caffeine*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 250 spectra of 7 reference samples from the substance/substance group *Caffeine*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Euro OTC | Caffeine  | 2910019-03 | 20247              | 50      |
| Caelo    | Caffeine  | 12317911   | 21089              | 40      |
| Caelo    | Caffeine  | 13233105   | 21456 <sup>†</sup> | 20      |
| Caelo    | Caffeine  | 13233104   | 21548 <sup>†</sup> | 20      |
| Euro OTC | Caffeine  | 1603009    | 22517              | 40      |
| Caelo    | Caffeine  | 15082303   | 22823              | 40      |
| Euro OTC | Caffeine  | 1703006    | 23140              | 40      |

- 146 479 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 86 spectra from 46 *Apo-Ident* customers from 39 batches from the substance/substance group *Caffeine*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier              | Substance | Batch         | Spectra |
|-----------------------|-----------|---------------|---------|
| Caelo                 | Caffeine  | 9301807       | 1       |
| Caelo                 | Caffeine  |               | 2       |
| Caelo                 | Caffeine  | 11076807      | 2       |
| Euro OTC              | Caffeine  | 1109017-01    | 2       |
| Caelo                 | Caffeine  | 11111111      | 1       |
| Caelo                 | Caffeine  | 12093402      | 2       |
| Anzag 03.05.2013      | Caffeine  | 1205047-01    | 1       |
| Caelo                 | Caffeine  | 12093410      | 2       |
| Euro OTC              | Caffeine  | 1211012-01    | 1       |
| Caelo                 | Caffeine  | 12093418      | 2       |
| Caelo                 | Caffeine  | 1211012-01    | 1       |
| Euro OTC              | Caffeine  | 1211012-02    | 1       |
| Caelo                 | Caffeine  | 12317902      | 1       |
| Caelo                 | Caffeine  | 12317904      | 2       |
| Caelo                 | Caffeine  | 12317906      | 1       |
| Caelo                 | Caffeine  | 12317909      | 7       |
| Caelo                 | Caffeine  | 12317914      | 2       |
| Euro OTC              | Caffeine  | 1307049-01    | 4       |
| Caelo                 | Caffeine  | 13233105      | 4       |
| Caelo                 | Caffeine  | 13233111      | 4       |
| Noweda                | Caffeine  | 1404026-01    | 1       |
| Euro OTC              | Caffeine  | 1411015-01    | 5       |
| Caelo                 | Caffeine  | 1503020-01    | 2       |
| Euro OTC              | Caffeine  | 1503020-01    | 6       |
| Euro OTC              | Caffeine  | 1503020-02    | 7       |
| Caelo                 | Caffeine  | 15054704      | 2       |
| Caelo                 | Caffeine  | 15054709      | 2       |
| Caelo                 | Caffeine  | 15082311      | 1       |
| Caelo                 | Caffeine  | 15375006      | 1       |
| Caelo                 | Caffeine  | 15375012      | 2       |
| Euro OTC              | Caffeine  | 1603009/01    | 1       |
| Euro OTC              | Caffeine  | 1603009-01    | 2       |
| Euro OTC              | Caffeine  | 160300901     | 1       |
| Phönix                | Caffeine  | 1603009-02    | 1       |
| Euro OTC              | Caffeine  | 1703006-01    | 1       |
| Euro OTC              | Caffeine  | 188921AX20    | 1       |
| Euro OTC              | Caffeine  | 26081406      | 1       |
| Caelo                 | Caffeine  | 3212E-01281   | 1       |
| Euro OTC              | Caffeine  | 325241AX20    | 1       |
| Gatt-Koller / Phoenix | Caffeine  | 5898/12135213 | 2       |
| EUro/AHD              | Caffeine  | 121012-01     | 1       |
| EUro/AHD              | Caffeine  | 1307049-01    | 1       |

- 69 547 spectra from 414 *Apo-Ident* customers from a total of 23 763 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Caffeine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Caffeine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 160           | 0              | 71 226        |
| Type B | 0              | 248           | 2              | 146 479       |
| Type C | 0              | 85            | 1              | 69 547        |

The substance/substance group *Caffeine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| Type B | 100.0000 % (> 99.9923 %) | 99.2000 % (> 98.0000 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 98.8372 % (> 95.3488 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20962     | 20962               | 0.00                         | 48.05                           |
| 21205     | 20962               | 6.68                         | 47.31                           |
| 21456     | 20962               | 6.48                         | 46.96                           |
| 21548     | 20962               | 3.12                         | 48.31                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Calcium ascorbate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20393-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Calcium ascorbate; Calcii ascorbas; Calcii ascorbinicum

### Special notes

When selecting the *Calcium ascorbate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Calcium ascorbate*:

| Supplier | Substance         | Batch    | Sample ID | Spectra | Certificate |
|----------|-------------------|----------|-----------|---------|-------------|
| Caelo    | Calcium ascorbate | 13105624 | 21313     | 40      | 20130620    |
| Euro OTC | Calcium ascorbate | 1612003  | 22916     | 40      | 20170110*   |
| Euro OTC | Calcium ascorbate | 1709005  | 23609     | 40      | 20170914*   |
| Euro OTC | Calcium ascorbate | 1709004  | 23611     | 40      | 20170914*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Calcium ascorbate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 160 spectra of 4 reference samples from the substance/substance group *Calcium ascorbate*.

| Supplier | Substance         | Batch      | Sample ID | Spectra |
|----------|-------------------|------------|-----------|---------|
| Caelo    | Calcium ascorbate | 10365208   | 20393     | 40      |
| Euro OTC | Calcium ascorbate | 1607033-01 | 22812     | 40      |
| Caelo    | Calcium ascorbate | 163111     | 23060     | 40      |
| Caelo    | Calcium ascorbate | 16311101   | 23518     | 40      |

- 146 569 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 11 spectra from 7 *Apo-Ident* customers from 11 batches from the substance/substance group *Calcium ascorbate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier                | Substance         | Batch         | Spectra |
|-------------------------|-------------------|---------------|---------|
| Caelo                   | Calcium ascorbate | 14340907      | 1       |
| Euro OTC                | Calcium ascorbate | L1502018-01   | 1       |
| Caelo                   | Calcium ascorbate | 15324708      | 1       |
| Burton Feingold         | Calcium ascorbate | L008415       | 1       |
| Euro OTC                | Calcium ascorbate | L1508017-01   | 1       |
| Caelo                   | Calcium ascorbate | L1502018-02   | 1       |
| Euro OTC                | Calcium ascorbate | L15218-2      | 1       |
| Caelo                   | Calcium ascorbate | 11159915      | 1       |
| Caelo                   | Calcium ascorbate | 12097406      | 1       |
| Caelo                   | Calcium ascorbate | 13105608      | 1       |
| Farmalabor / Farmalabor | Calcium ascorbate | P1104931-000A | 1       |

- 69 622 spectra from 414 *Apo-Ident* customers from a total of 23 790 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Calcium ascorbate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Calcium ascorbate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 160           | 0              | 146 569       |
| <b>Type C</b> | 0              | 10            | 1              | 69 622        |

The substance/substance group *Calcium ascorbate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.2500 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21313     | 23609               | 1.44                         | 41.44                           |
| 22916     | 22916               | 0.00                         | 42.81                           |
| 23609     | 23609               | 0.00                         | 41.97                           |
| 23611     | 23611               | 0.00                         | 42.00                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Calcium citrate tetrahydrate</b>                             |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20013-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Calcium citrate tetrahydrate; Calcii citras tetrahydricus; Calcii citricum

### Special notes

When selecting the *Calcium citrate tetrahydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Calcium citrate tetrahydrate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Euro OTC | Calcium citrate ... | 1305018-01 | 21249     | 40      | 20130528    |
| Caelo    | Calcium citrate ... | 13391203   | 21486     | 40      | 20131205    |
| Euro OTC | Calcium citrate ... | 1509039    | 21931     | 40      | 20151013*   |
| Euro OTC | Calcium citrate ... | 1509039-01 | 22255     | 40      | 20151013    |
| Euro OTC | Calcium citrate ... | 1701001    | 22995     | 40      | 20170124*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Calcium citrate tetrahydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 250 spectra of 7 reference samples from the substance/substance group *Calcium citrate tetrahydrate*.

| Supplier | Substance                    | Batch      | Sample ID          | Spectra |
|----------|------------------------------|------------|--------------------|---------|
| Caelo    | Calcium citrate tetrahydrate | 90034189   | 20013              | 60      |
| Caelo    | Calcium citrate tetrahydrate | 13391203   | 21320              | 40      |
| Euro OTC | Calcium citrate tetrahydrate | 1509039    | 21931 <sup>†</sup> | 20      |
| Euro OTC | Calcium citrate tetrahydrate | 1509039-01 | 22255 <sup>†</sup> | 20      |
| Euro OTC | Calcium citrate tetrahydrate | 1606001    | 22681              | 40      |
| Euro OTC | Calcium citrate tetrahydrate | 1707025    | 23606              | 40      |
| Caelo    | Calcium citrate tetrahydrate | 171768     | 23651              | 30      |

- 146 479 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 165 spectra from 71 *Apo-Ident* customers from 85 batches from the substance/substance group *Calcium citrate tetrahydrate*.

| Supplier                   | Substance                    | Batch       | Spectra |
|----------------------------|------------------------------|-------------|---------|
| Caelo                      | Calcium citrate tetrahydrate |             | 3       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1402003-01  | 3       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1509039-02  | 6       |
| Caelo                      | Calcium citrate tetrahydrate | 15177702    | 2       |
| Caelo                      | Calcium citrate tetrahydrate | 15375703    | 1       |
| GEHE                       | Calcium citrate tetrahydrate | 21022141/3  | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 50/6        | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1408017-01  | 3       |
| Caelo                      | Calcium citrate tetrahydrate | 13391203    | 3       |
| Caelo                      | Calcium citrate tetrahydrate | 13391205    | 3       |
| Caelo                      | Calcium citrate tetrahydrate | 11349325    | 2       |
| Caelo                      | Calcium citrate tetrahydrate | 11168806    | 5       |
| Caelo                      | Calcium citrate tetrahydrate | 11061402    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 12310418    | 2       |
| Caelo                      | Calcium citrate tetrahydrate | 130501801   | 2       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1305018-01  | 5       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1305018-02  | 3       |
| Alliance Health 23.10.2... | Calcium citrate tetrahydrate | 1402003-01  | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 14020031    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 1408017-01  | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 140801701   | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 14133303    | 1       |
| Gehe Kassel                | Calcium citrate tetrahydrate | 14133307    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 14133310    | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1502012-01  | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1502012-02  | 1       |
| EuRho                      | Calcium citrate tetrahydrate | 1502012-02  | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1502012-2   | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1502021-02  | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 1509039-01  | 2       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1509039-01  | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 15177701    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 15177703    | 3       |
| Euro OTC                   | Calcium citrate tetrahydrate | 15177704    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 15375707    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 15375712    | 2       |
| Caelo                      | Calcium citrate tetrahydrate | 15375713    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 16021502    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 16056501    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 16056504    | 3       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1606001-01  | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1606001-02  | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1701001-01  | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 2114M1209   | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 3006222     | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 3512U-01209 | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1040896     | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1107012-01  | 1       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1107012-02  | 4       |
| Fagron                     | Calcium citrate tetrahydrate | 413031/2    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 11168813    | 1       |
| Caelo                      | Calcium citrate tetrahydrate | 11349304    | 2       |
| Caelo                      | Calcium citrate tetrahydrate | 11349309    | 2       |
| Euro OTC                   | Calcium citrate tetrahydrate | 1009030-01  | 1       |

*continued on the next page*

continued from previous page

| Supplier        | Substance                    | Batch          | Spectra |
|-----------------|------------------------------|----------------|---------|
| Euro OTC        | Calcium citrate tetrahydrate | 1111036-01     | 3       |
| Phönix          | Calcium citrate tetrahydrate | 1111036-01     | 2       |
| Euro OTC        | Calcium citrate tetrahydrate | 1058904        | 1       |
| Phönix          | Calcium citrate tetrahydrate | 1207006-01     | 3       |
| Euro OTC        | Calcium citrate tetrahydrate | 1207006-01     | 4       |
| Euro OTC        | Calcium citrate tetrahydrate | 1211007-01     | 5       |
| Sanacorp        | Calcium citrate tetrahydrate | 1211007-01     | 1       |
| EuRho/Jenne     | Calcium citrate tetrahydrate | 1211007-01     | 1       |
| Caelo           | Calcium citrate tetrahydrate | 121100701      | 1       |
| Caelo           | Calcium citrate tetrahydrate | 12310401       | 2       |
| Caelo           | Calcium citrate tetrahydrate | 12310407       | 2       |
| Caelo           | Calcium citrate tetrahydrate | 12310413       | 4       |
| Euro OTC        | Calcium citrate tetrahydrate | 13031204       | 1       |
| Phönix          | Calcium citrate tetrahydrate | 1305018-01     | 1       |
| Fagron          | Calcium citrate tetrahydrate | 13d16-n06      | 1       |
| Caelo           | Calcium citrate tetrahydrate | 92192429       | 1       |
| Caelo           | Calcium citrate tetrahydrate | 92457399       | 1       |
| Sanacorp        | Calcium citrate tetrahydrate | 111103601      | 1       |
| Caelo           | Calcium citrate tetrahydrate | 11168803       | 1       |
| Caelo           | Calcium citrate tetrahydrate | 11349301       | 1       |
| Noweda          | Calcium citrate tetrahydrate | 11349309       | 1       |
| Post-Apotheke   | Calcium citrate tetrahydrate | 11349313       | 1       |
| Caelo           | Calcium citrate tetrahydrate | 11349313       | 2       |
| Caelo           | Calcium citrate tetrahydrate | 11349315       | 1       |
| Caelo           | Calcium citrate tetrahydrate | 11349318       | 4       |
| Caelo           | Calcium citrate tetrahydrate | 11349320       | 1       |
| Phönix 07.03.13 | Calcium citrate tetrahydrate | 11349325       | 1       |
| Elementar       | Calcium citrate tetrahydrate | 11602007228939 | 1       |
| Caelo           | Calcium citrate tetrahydrate | 1168806        | 1       |
| Caelo           | Calcium citrate tetrahydrate | 1168813        | 1       |
| Gehe 12.04.2013 | Calcium citrate tetrahydrate | 11K04-N09      | 1       |
| Caelo           | Calcium citrate tetrahydrate | 12310401       | 1       |
| Caelo           | Calcium citrate tetrahydrate | 12310402       | 2       |
| Caelo           | Calcium citrate tetrahydrate | 12310403       | 3       |
| Caelo           | Calcium citrate tetrahydrate | 12310406       | 3       |
| Caelo           | Calcium citrate tetrahydrate | 12310411       | 2       |
| Caelo           | Calcium citrate tetrahydrate | 12310417       | 3       |
| Caelo           | Calcium citrate tetrahydrate | 133912042x     | 1       |
| Caelo           | Calcium citrate tetrahydrate | 19061315       | 1       |
| Fagron          | Calcium citrate tetrahydrate | 13D16-N06      | 1       |
| Jungbunzlauer   | Calcium citrate tetrahydrate | 2012290954     | 1       |
| Caelo           | Calcium citrate tetrahydrate | 71356168       | 1       |

- 69 468 spectra from 414 *Apo-Ident* customers from a total of 23 718 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Calcium citrate tetrahydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Calcium citrate tetrahydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct



or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 186           | 14             | 71 186        |
| <b>Type B</b> | 0              | 241           | 9              | 146 479       |
| <b>Type C</b> | 0              | 145           | 20             | 69 468        |

The substance/substance group *Calcium citrate tetrahydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate        |
|---------------|--------------------------|-------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 93.0000 % (> 91.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 96.4000 % (> 95.2000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 87.8788 % (> 86.0606 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21249     | 21931               | 3.65                         | 55.89                           |
| 21486     | 22995               | 5.69                         | 46.65                           |
| 21931     | 21931               | 0.00                         | 55.89                           |
| 22255     | 21931               | 3.01                         | 55.11                           |
| 22995     | 22995               | 0.00                         | 52.15                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Calcium gluconate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20871-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Calcium gluconate; Calcii gluconas; Calcii gluconicum

### Special notes

When selecting the *Calcium gluconate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Calcium gluconate*:

| Supplier | Substance         | Batch      | Sample ID | Spectra | Certificate        |
|----------|-------------------|------------|-----------|---------|--------------------|
| Caelo    | Calcium gluconate | 12236502   | 20871     | 40      | 1401575            |
| Euro OTC | Calcium gluconate | 1304012-01 | 21283     | 40      | AR-15-FG-008127-01 |
| Caelo    | Calcium gluconate | 12335829   | 21312     | 40      | 20121121           |
| Euro OTC | Calcium gluconate | 1407041-01 | 21821     | 40      | 20140818           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Calcium gluconate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Calcium gluconate*.

| Supplier | Substance         | Batch      | Sample ID          | Spectra |
|----------|-------------------|------------|--------------------|---------|
| Euro OTC | Calcium gluconate | 1005044-01 | 20270              | 40      |
| Euro OTC | Calcium gluconate | 1407041-01 | 21821 <sup>†</sup> | 20      |
| Euro OTC | Calcium gluconate | 1606034    | 22699              | 40      |
| Caelo    | Calcium gluconate | 154356     | 23360              | 40      |

- 146 589 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 91 spectra from 49 *Apo-Ident* customers from 42 batches from the substance/substance group *Calcium gluconate*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier              | Substance         | Batch            | Spectra |
|-----------------------|-------------------|------------------|---------|
| Euro OTC              | Calcium gluconate | 1407041-01       | 3       |
| Euro OTC              | Calcium gluconate | 1209006-01       | 12      |
| Fagron                | Calcium gluconate | 12/13-N04        | 1       |
| EuRho                 | Calcium gluconate | 12090006-01      | 1       |
| Euro OTC              | Calcium gluconate | 1304012-01       | 7       |
| Euro/Gehe             | Calcium gluconate | 1304012-01       | 1       |
| Euro OTC              | Calcium gluconate | 1304012-02       | 7       |
| Euro OTC              | Calcium gluconate | 130401202        | 1       |
| Euro OTC              | Calcium gluconate | 140704101        | 1       |
| Euro OTC              | Calcium gluconate | 140704102        | 1       |
| Euro OTC              | Calcium gluconate | 1407041-02       | 9       |
| Caelo                 | Calcium gluconate | 1407041-02       | 1       |
| Caelo                 | Calcium gluconate | 140704102        | 1       |
| Berkel AHK            | Calcium gluconate | 14085407         | 2       |
| Caelo                 | Calcium gluconate | 14230706         | 1       |
| Fagron                | Calcium gluconate | 14D11-B04        | 1       |
| Fagron                | Calcium gluconate | 14D11-B04-292997 | 1       |
| Fagron                | Calcium gluconate | 14D11-B04-294136 | 1       |
| Caelo                 | Calcium gluconate | 15126301         | 2       |
| Caelo                 | Calcium gluconate | 15324807         | 1       |
| Caelo                 | Calcium gluconate | 15435601         | 1       |
| Caelo                 | Calcium gluconate | 15435607         | 1       |
| Caelo                 | Calcium gluconate | 15435611         | 1       |
| Caelo                 | Calcium gluconate | 15435619         | 1       |
| Caelo                 | Calcium gluconate | 1543601          | 1       |
| Fagron                | Calcium gluconate | 15D13-B98-307445 | 1       |
| Phönix                | Calcium gluconate | 1606034-01       | 1       |
| Euro OTC              | Calcium gluconate | 1606034-01       | 4       |
| Euro OTC              | Calcium gluconate | Ch1407041-01     | 1       |
| Euro OTC              | Calcium gluconate | 513-Q1211        | 1       |
| Gatt-Koller / Phoenix | Calcium gluconate | 550/03141214     | 1       |
| Fagron                | Calcium gluconate | 10G22-N12        | 1       |
| Euro OTC              | Calcium gluconate | 1105027          | 1       |
| Euro OTC              | Calcium gluconate | 1105027-01       | 3       |
| Euro OTC              | Calcium gluconate | 1105027-02       | 3       |
| Fagron                | Calcium gluconate | 1105027-02       | 1       |
| Caelo                 | Calcium gluconate | 11121607         | 1       |
| Euro OTC              | Calcium gluconate | 115027-01        | 1       |
| Euro OTC              | Calcium gluconate | 1209006          | 1       |
| gehe                  | Calcium gluconate | 1209006-01       | 1       |
| Eurho/Sns             | Calcium gluconate | 1209006-01       | 1       |
| Caelo                 | Calcium gluconate | 12335810         | 1       |
| Caelo                 | Calcium gluconate | 12335813         | 1       |
| Caelo                 | Calcium gluconate | 1235813          | 1       |
| Fagron                | Calcium gluconate | 12D17-N01        | 1       |
| Caelo                 | Calcium gluconate | 14085405         | 1       |
| Euro OTC              | Calcium gluconate | 20270912-1       | 1       |
| Euro OTC              | Calcium gluconate | Ch1304012        | 1       |
| Finze                 | Calcium gluconate | 917857359        | 1       |

- 69 542 spectra from 414 *Apo-Ident* customers from a total of 23 759 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Calcium gluconate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Calcium gluconate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 160           | 0              | 71 226        |
| Type B | 0              | 130           | 10             | 146 589       |
| Type C | 0              | 82            | 9              | 69 542        |

The substance/substance group *Calcium gluconate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| Type B | 100.0000 % (> 99.9923 %) | 92.8571 % (> 90.7143 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 90.1099 % (> 86.8132 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20871     | 20871               | 0.00                         | 38.92                           |
| 21283     | 21283               | 0.00                         | 29.64                           |
| 21312     | 20871               | 5.88                         | 39.49                           |
| 21821     | 21283               | 2.83                         | 29.61                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Calcium glycerophosphate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20352-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Calcium glycerophosphate; Calcii glycerinophosphoricum; Calcii glycerophosphas

### Special notes

When selecting the *Calcium glycerophosphate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Calcium glycerophosphate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Caelo    | Calcium glycerop... | 12012417         | 20771     | 40      | 20120131           |
| Fagron   | Calcium glycerop... | 13I17-N04        | 21234     | 40      | 20131016           |
| Caelo    | Calcium glycerop... | 13007912         | 21311     | 40      | 20130124           |
| Caelo    | Calcium glycerop... | 14341007         | 21969     | 40      | AR-16-FG-005932-01 |
| Fagron   | Calcium glycerop... | 15B03-B03-305050 | 21978     | 40      | 1706313            |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Calcium glycerophosphate*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 360 spectra of 10 reference samples from the substance/substance group *Calcium glycerophosphate*.

| Supplier | Substance                | Batch            | Sample ID          | Spectra |
|----------|--------------------------|------------------|--------------------|---------|
| Caelo    | Calcium glycerophosphate | 11160607         | 20352              | 40      |
| Caelo    | Calcium glycerophosphate | 12012403         | 20507              | 40      |
| Caelo    | Calcium glycerophosphate | 12012411         | 20605              | 40      |
| Caelo    | Calcium glycerophosphate | 12012405         | 20606              | 40      |
| Caelo    | Calcium glycerophosphate | 12012411         | 20679              | 40      |
| Caelo    | Calcium glycerophosphate | 12012417         | 20762              | 40      |
| Caelo    | Calcium glycerophosphate | 12012413         | 20763              | 40      |
| Caelo    | Calcium glycerophosphate | 14341007         | 21969 <sup>†</sup> | 20      |
| Fagron   | Calcium glycerophosphate | 15B03-B03-305050 | 21978 <sup>†</sup> | 20      |
| Caelo    | Calcium glycerophosphate | 162310           | 23361              | 40      |

- 146 369 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



provided by the customer regarding manufacturer and batch number.

- 73 spectra from 39 *Apo-Ident* customers from 44 batches from the substance/substance group *Calcium glycerophosphate*.

| Supplier           | Substance                | Batch            | Spectra |
|--------------------|--------------------------|------------------|---------|
| Caelo              | Calcium glycerophosphate | 13007914         | 2       |
| Fagron             | Calcium glycerophosphate | 13/17-N04        | 2       |
| Caelo              | Calcium glycerophosphate | 13007908         | 1       |
| Caelo              | Calcium glycerophosphate | 13007912         | 2       |
| Caelo              | Calcium glycerophosphate | 13007919         | 1       |
| Caelo              | Calcium glycerophosphate | 13007922         | 1       |
| Fagron             | Calcium glycerophosphate | 1314000019       | 1       |
| Caelo              | Calcium glycerophosphate | 1341001          | 1       |
| Fagron             | Calcium glycerophosphate | 13A18N02         | 2       |
| Fagron             | Calcium glycerophosphate | 1317-N04         | 2       |
| Fagron             | Calcium glycerophosphate | 13A18-N02        | 5       |
| Caelo              | Calcium glycerophosphate | 1431001          | 1       |
| Caelo              | Calcium glycerophosphate | 14341007         | 4       |
| Caelo              | Calcium glycerophosphate | 14341010         | 1       |
| Caelo              | Calcium glycerophosphate | 14341012         | 2       |
| Caelo              | Calcium glycerophosphate | 14341009         | 1       |
| Caelo              | Calcium glycerophosphate | 14341013         | 1       |
| Sanacorp           | Calcium glycerophosphate | 14341015         | 1       |
| Caelo              | Calcium glycerophosphate | 14341015         | 1       |
| Caelo              | Calcium glycerophosphate | 14347101         | 2       |
| Fagron             | Calcium glycerophosphate | 14B10B02         | 1       |
| Fagron             | Calcium glycerophosphate | 14B10-B02        | 1       |
| Fagron             | Calcium glycerophosphate | 14B10-B02-291642 | 2       |
| Fagron             | Calcium glycerophosphate | 14B10-B02-296841 | 4       |
| Caelo              | Calcium glycerophosphate | 14B10-B02-296841 | 1       |
| Fagron             | Calcium glycerophosphate | 14B10-B02-296842 | 1       |
| Fagron             | Calcium glycerophosphate | 15B03B03         | 1       |
| Caelo              | Calcium glycerophosphate | 15B03-B03-305050 | 1       |
| Fagron             | Calcium glycerophosphate | 15B03-B03        | 1       |
| Caelo              | Calcium glycerophosphate | 15B03B03305050   | 1       |
| Fagron             | Calcium glycerophosphate | 15B03-B03-305050 | 2       |
| Caelo              | Calcium glycerophosphate | 16231001         | 2       |
| Caelo              | Calcium glycerophosphate | 16231004         | 2       |
| Caelo              | Calcium glycerophosphate | 16231005         | 1       |
| Caelo              | Calcium glycerophosphate | 16231006         | 2       |
| Caelo              | Calcium glycerophosphate | 301500           | 1       |
| Fagron             | Calcium glycerophosphate | 3115A-01212      | 1       |
| Fagron             | Calcium glycerophosphate | 5212M-01212      | 1       |
| Fagron             | Calcium glycerophosphate | 11G19-N05        | 1       |
| Fagron             | Calcium glycerophosphate | 12/18-N06        | 2       |
| Caelo              | Calcium glycerophosphate | 12012406         | 1       |
| Caelo              | Calcium glycerophosphate | 12012413         | 2       |
| Fagron             | Calcium glycerophosphate | 1216000005       | 1       |
| Fagron             | Calcium glycerophosphate | 12I18-N06        | 3       |
| Caelo              | Calcium glycerophosphate | 13007902         | 1       |
| Caelo              | Calcium glycerophosphate | 13A18-No2        | 1       |
| Gatt-Koller/Kwizda | Calcium glycerophosphate | 4007/09123812    | 1       |

- 69 560 spectra from 414 *Apo-Ident* customers from a total of 23 758 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),

the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Calcium glycerophosphate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Calcium glycerophosphate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 200           | 0              | 71 186        |
| Type B | 0              | 357           | 3              | 146 369       |
| Type C | 0              | 53            | 20             | 69 560        |

The substance/substance group *Calcium glycerophosphate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 99.1667 % (> 98.3333 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 72.6027 % (> 68.4932 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20771     | 21969               | 15.91                        | 33.77                           |
| 21234     | 21969               | 3.40                         | 31.31                           |
| 21311     | 21969               | 4.09                         | 30.75                           |
| 21969     | 21969               | 0.00                         | 31.65                           |
| 21978     | 21978               | 0.00                         | 34.02                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Calcium lactate pentahydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20745-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Calcium lactate pentahydrate; Calcii lactas pentahydricus; Calcii lacticum pentahydricum

### Special notes

When selecting the *Calcium lactate pentahydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Calcium lactate pentahydrate*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate        |
|----------|---------------------|-----------|-----------|---------|--------------------|
| Fagron   | Calcium lactate ... | 12E10-N03 | 20745     | 40      | 20120704           |
| Fagron   | Calcium lactate ... | 12I12-N06 | 21232     | 40      | AR-15-FG-007939-01 |
| Caelo    | Calcium lactate ... | 15101401  | 21909     | 40      | 20150407           |
| Caelo    | Calcium lactate ... | 15101405  | 22263     | 40      | 20150407           |
| Caelo    | Calcium lactate ... | 161313    | 22445     | 40      | 20160513*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Calcium lactate pentahydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 6 reference samples from the substance/substance group *Calcium lactate pentahydrate*.

| Supplier | Substance                    | Batch            | Sample ID          | Spectra |
|----------|------------------------------|------------------|--------------------|---------|
| Fagron   | Calcium lactate pentahydrate | pending          | 20516              | 40      |
| Caelo    | Calcium lactate pentahydrate | 15101401         | 21909 <sup>†</sup> | 20      |
| Caelo    | Calcium lactate pentahydrate | 15101405         | 22263 <sup>†</sup> | 20      |
| Caelo    | Calcium lactate pentahydrate | 161313           | 22445 <sup>†</sup> | 20      |
| Fagron   | Calcium lactate pentahydrate | 14H01-B05-323830 | 23566              | 40      |
| Caelo    | Calcium lactate pentahydrate | 171377           | 23642              | 40      |

- 146 549 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 38 spectra from 16 *Apo-Ident* customers from 24 batches from the substance/substance group *Calcium lactate pentahydrate*.

| Supplier        | Substance                    | Batch            | Spectra |
|-----------------|------------------------------|------------------|---------|
| Caelo           | Calcium lactate pentahydrate | 11369606         | 1       |
| Fagron          | Calcium lactate pentahydrate | 12I12-N06        | 2       |
| Caelo           | Calcium lactate pentahydrate | 13080804         | 2       |
| Caelo           | Calcium lactate pentahydrate | 13080805         | 2       |
| Fagron          | Calcium lactate pentahydrate | 13L18B04         | 1       |
| Fagron          | Calcium lactate pentahydrate | 13L18-B04-295541 | 3       |
| Fagron          | Calcium lactate pentahydrate | 14H01-B05        | 1       |
| Caelo           | Calcium lactate pentahydrate | 14H01B05300502   | 1       |
| Fagron/Sanacorp | Calcium lactate pentahydrate | 14H01-B05        | 1       |
| Caelo           | Calcium lactate pentahydrate | 15101409         | 1       |
| Caelo           | Calcium lactate pentahydrate | 15101411         | 2       |
| Caelo           | Calcium lactate pentahydrate | 15227804         | 2       |
| Caelo           | Calcium lactate pentahydrate | 16131307         | 1       |
| Shop            | Calcium lactate pentahydrate | 1111001829       | 1       |
| Caelo           | Calcium lactate pentahydrate | 11369610         | 1       |
| Caelo           | Calcium lactate pentahydrate | 11369614         | 2       |
| Caelo           | Calcium lactate pentahydrate | 11369618         | 1       |
| Krämer&Martin   | Calcium lactate pentahydrate | 11612009053019   | 1       |
| Fagron          | Calcium lactate pentahydrate | 11126-N15        | 1       |
| Fagron          | Calcium lactate pentahydrate | 12/12-N06        | 1       |
| Fagron          | Calcium lactate pentahydrate | 12C15-N02        | 3       |
| Caelo           | Calcium lactate pentahydrate | 12C15-N02        | 2       |
| Caelo           | Calcium lactate pentahydrate | 12E10-N03        | 1       |
| Fagron          | Calcium lactate pentahydrate | 12I12-N01        | 1       |
| Caelo           | Calcium lactate pentahydrate | 13080802         | 2       |
| Stockmeier Food | Calcium lactate pentahydrate | 2012331885       | 1       |

- 69 595 spectra from 414 *Apo-Ident* customers from a total of 23 778 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Calcium lactate pentahydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Calcium lactate pentahydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 180           | 0              | 146 549       |
| <b>Type C</b> | 0              | 37            | 1              | 69 595        |

The substance/substance group *Calcium lactate pentahydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.6667 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 97.3684 % (> 89.4737 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20745     | 21232               | 6.82                         | 48.48                           |
| 21232     | 21232               | 0.00                         | 45.17                           |
| 21909     | 21232               | 3.46                         | 47.51                           |
| 22263     | 21232               | 7.71                         | 44.85                           |
| 22445     | 22445               | 0.00                         | 49.00                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Calcium orotate dihydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20418-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Calcium orotate dihydrate; Calcii orotas; Calcii oroticum

### Special notes

When selecting the *Calcium orotate dihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Calcium orotate dihydrate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Fagron   | Calcium orotate ... | 12L04-N07  | 20824     | 40      | 20121207    |
| Fagron   | Calcium orotate ... | 13J23-N05  | 21227     | 40      | 20131111    |
| Euro OTC | Calcium orotate ... | 1401006-01 | 21245     | 40      | 1412540     |
| Euro OTC | Calcium orotate ... | 1603003    | 22520     | 40      | 20160329*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Calcium orotate dihydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 5 reference samples from the substance/substance group *Calcium orotate dihydrate*.

| Supplier    | Substance                 | Batch            | Sample ID | Spectra |
|-------------|---------------------------|------------------|-----------|---------|
| Pharmorgana | Calcium orotate dihydrate | 1000139407       | 20418     | 40      |
| Euro OTC    | Calcium orotate dihydrate | 1009035-01       | 20535     | 40      |
| Euro OTC    | Calcium orotate dihydrate | 1009035-01       | 20814     | 40      |
| Euro OTC    | Calcium orotate dihydrate | 1411003          | 22519     | 40      |
| Fagron      | Calcium orotate dihydrate | 16F13-B04-324144 | 23574     | 40      |

- 146 529 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 8 spectra from 3 *Apo-Ident* customers from 6 batches from the substance/substance group *Calcium orotate dihydrate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier             | Substance                 | Batch      | Spectra |
|----------------------|---------------------------|------------|---------|
| Euro OTC             | Calcium orotate dihydrate | 1009035-01 | 2       |
| Microsin Pharmorgana | Calcium orotate dihydrate | ORC00413   | 1       |
| Euro OTC             | Calcium orotate dihydrate | 1203037-01 | 2       |
| Euro OTC             | Calcium orotate dihydrate | 1401006-01 | 1       |
| Pharmorgana          | Calcium orotate dihydrate | ORC00113   | 1       |
| Pharmorgana          | Calcium orotate dihydrate | ORC00213   | 1       |

- 69 625 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Calcium orotate dihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Calcium orotate dihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 111           | 89             | 146 529       |
| <b>Type C</b> | 0              | 8             | 0              | 69 625        |

The substance/substance group *Calcium orotate dihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 55.5000 % (> 54.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20824     | 21245               | 5.07                         | 64.29                           |
| 21227     | 21245               | 2.46                         | 63.89                           |
| 21245     | 21245               | 0.00                         | 64.54                           |
| 22520     | 22520               | 0.00                         | 64.32                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Calcium pantothenate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20395-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Calcium pantothenate; Calcii panthothenas; Calcii panthothenicum

### Special notes

When selecting the *Calcium pantothenate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Calcium pantothenate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Fagron   | Calcium pantothe... | 13H28-N11  | 21233     | 40      | 20130916    |
| Euro OTC | Calcium pantothe... | 1305034-01 | 21243     | 40      | 20130617    |
| Caelo    | Calcium pantothe... | 14208012   | 21765     | 40      | 20140722    |
| Euro OTC | Calcium pantothe... | 1509024    | 21901     | 40      | 20151005*   |
| Euro OTC | Calcium pantothe... | 1603042    | 22551     | 40      | 20160429*   |
| Euro OTC | Calcium pantothe... | 1607023    | 22691     | 40      | 20160809*   |
| Euro OTC | Calcium pantothe... | 1702018    | 23153     | 40      | 20170330*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 280 spectra of 7 reference samples from the substance/substance group *Calcium pantothenate*. These samples are listed above in the [calibration samples](#) section.
- 71 106 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 160 spectra of 5 reference samples from the substance/substance group *Calcium pantothenate*.

| Supplier | Substance            | Batch     | Sample ID          | Spectra |
|----------|----------------------|-----------|--------------------|---------|
| Fagron   | Calcium pantothenate | 11J20-N01 | 20395              | 40      |
| Fagron   | Calcium pantothenate | 10I22-N05 | 20444              | 40      |
| Caelo    | Calcium pantothenate | 14208012  | 21765 <sup>†</sup> | 20      |
| Euro OTC | Calcium pantothenate | 1509024   | 21901 <sup>†</sup> | 20      |
| Caelo    | Calcium pantothenate | 162516    | 23363              | 40      |

- 146 569 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 65 spectra from 33 *Apo-Ident* customers from 42 batches from the substance/substance group *Calcium pantothenate*.

| Supplier              | Substance            | Batch            | Spectra |
|-----------------------|----------------------|------------------|---------|
| Caelo                 | Calcium pantothenate | 14208004         | 1       |
| Caelo                 | Calcium pantothenate | 15143914         | 1       |
| Caelo                 | Calcium pantothenate | 12340832         | 1       |
| Caelo                 | Calcium pantothenate | 12340846         | 1       |
| Fagron                | Calcium pantothenate | 13H28N11         | 1       |
| Fagron                | Calcium pantothenate | 13H28-N11        | 1       |
| Fagron                | Calcium pantothenate | 14G02-B10-297373 | 1       |
| Fagron                | Calcium pantothenate | 14G02-B10-301624 | 1       |
| Euroo/Anzag           | Calcium pantothenate | 1509024-01       | 2       |
| Fagron                | Calcium pantothenate | 1111110405       | 1       |
| Caelo                 | Calcium pantothenate | 11105731         | 1       |
| Fagron                | Calcium pantothenate | 11L20-N11        | 1       |
| Caelo                 | Calcium pantothenate | 12340808         | 3       |
| Caelo                 | Calcium pantothenate | 12340809         | 1       |
| Fagron                | Calcium pantothenate | 12G05-N12        | 1       |
| Fagron                | Calcium pantothenate | 13B22-N01        | 1       |
| Euro OTC              | Calcium pantothenate | 5121405          | 1       |
| Caelo                 | Calcium pantothenate | 8041407          | 1       |
| Euro OTC              | Calcium pantothenate | 10021505         | 1       |
| Caelo                 | Calcium pantothenate | 12340859         | 1       |
| Euro OTC              | Calcium pantothenate | 1312027-01       | 3       |
| Euro OTC              | Calcium pantothenate | 1305034-01       | 4       |
| Euro OTC              | Calcium pantothenate | 1410011-01       | 1       |
| Caelo                 | Calcium pantothenate | 1410011-01       | 1       |
| Euro OTC              | Calcium pantothenate | 1410011-02       | 3       |
| Caelo                 | Calcium pantothenate | 1410011-02       | 1       |
| Noweda                | Calcium pantothenate | 14208012         | 1       |
| Euro OTC              | Calcium pantothenate | 1509024-01       | 2       |
| Fagron                | Calcium pantothenate | 14G02-B10        | 1       |
| Caelo                 | Calcium pantothenate | 1509024-01       | 1       |
| Euro OTC              | Calcium pantothenate | 1603042-01       | 3       |
| Caelo                 | Calcium pantothenate | 1607023-01       | 2       |
| Gehe                  | Calcium pantothenate | 1004024-01       | 1       |
| Caelo                 | Calcium pantothenate | 1013Q-03022      | 1       |
| Euro OTC              | Calcium pantothenate | 1111025-01       | 3       |
| Fagron                | Calcium pantothenate | 1111025-01       | 1       |
| Euro OTC              | Calcium pantothenate | 1209022-01       | 1       |
| Daiichi               | Calcium pantothenate | 1209022-01       | 1       |
| Euro OTC              | Calcium pantothenate | 1209022-02pzn    | 1       |
| Caelo                 | Calcium pantothenate | 27111303         | 1       |
| Caelo                 | Calcium pantothenate | 12236622         | 1       |
| Euro OTC              | Calcium pantothenate | 120902202        | 1       |
| Euro OTC              | Calcium pantothenate | 1209022-02       | 1       |
| Caelo                 | Calcium pantothenate | 12340819         | 2       |
| Fagron                | Calcium pantothenate | 12F19-N07        | 1       |
| Euro OTC              | Calcium pantothenate | 130503401        | 1       |
| Euro OTC              | Calcium pantothenate | 17021401         | 1       |
| Gatt-Koller / Phoenix | Calcium pantothenate | 3783/09112912    | 1       |

- 69 568 spectra from 414 *Apo-Ident* customers from a total of 23 760 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).



## Validation results

The validation runs checked whether the substance/substance group *Calcium pantothenate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Calcium pantothenate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 280           | 0              | 71 106        |
| Type B | 0              | 160           | 0              | 146 569       |
| Type C | 0              | 62            | 3              | 69 568        |

The substance/substance group *Calcium pantothenate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.8571 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.2500 %) |
| Type C | 100.0000 % (> 99.8813 %) | 95.3846 % (> 90.7692 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21233     | 23153               | 5.84                         | 17.72                           |
| 21243     | 23153               | 10.08                        | 16.27                           |
| 21765     | 23153               | 10.17                        | 17.08                           |
| 21901     | 21901               | 0.00                         | 22.15                           |
| 22551     | 22551               | 0.00                         | 15.25                           |
| 22691     | 22691               | 0.00                         | 14.12                           |
| 23153     | 23153               | 0.00                         | 18.10                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Camphor**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20028-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Camphor; Camphora

### Special notes

When selecting the *Camphor* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Camphor*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Euro OTC | Camphor   | 1406029-01       | 21599     | 40      | 20140708    |
| Fagron   | Camphor   | 14E19-B07-300365 | 22256     | 40      | 20140527    |
| Caelo    | Camphor   | 15316801         | 22279     | 40      | 20151029    |
| Caelo    | Camphor   | 162354           | 23065     | 40      | 20160809*   |
| Caelo    | Camphor   | 170043           | 23310     | 40      | 20170220*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Camphor*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 290 spectra of 9 reference samples from the substance/substance group *Camphor*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Caelo    | Camphor   | 82383109         | 20028              | 30      |
| Euro OTC | Camphor   | 2906016-02       | 20189              | 40      |
| Caelo    | Camphor   | 11074503         | 20287              | 40      |
| Euro OTC | Camphor   | 1106007-02       | 20328              | 40      |
| Euro OTC | Camphor   | 1406029-01       | 21599 <sup>†</sup> | 20      |
| Fagron   | Camphor   | 14E19-B07-300365 | 22256 <sup>†</sup> | 20      |
| Caelo    | Camphor   | 15316801         | 22279 <sup>†</sup> | 20      |
| Caelo    | Camphor   | 16209309         | 23408              | 40      |
| Fagron   | Camphor   | 16E23-B08-336937 | 23589              | 40      |

- 146 439 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 341 spectra from 172 *Apo-Ident* customers from 160 batches from the substance/substance group *Camphor*.

| Supplier                   | Substance | Batch               | Spectra |
|----------------------------|-----------|---------------------|---------|
| Euro OTC                   | Camphor   | 113Q-01221          | 1       |
| Caelo                      | Camphor   | 3091203             | 1       |
| Caelo                      | Camphor   | 312M-01219          | 1       |
| Caelo                      | Camphor   | 315E-01221          | 1       |
| Caelo                      | Camphor   | 4031503             | 1       |
| Caelo                      | Camphor   | 4101303             | 1       |
| Klenk                      | Camphor   | 444A160817          | 2       |
| Sanacorp                   | Camphor   | 444A130115          | 1       |
| Klenk                      | Camphor   | 444A140526          | 2       |
| xxx                        | Camphor   | 709E-01221          | 1       |
| Caelo                      | Camphor   | 713A-01221          | 1       |
| Fagron                     | Camphor   | 8082014A            | 1       |
| Caesar/Noweda              | Camphor   | 1032                | 1       |
| Caelo                      | Camphor   | 1087                | 1       |
| Euro OTC                   | Camphor   | 1101029-02/Ch241011 | 1       |
| Post-Apotheke 22.01.2013   | Camphor   | 11032012            | 1       |
| Caesar & Loretz GmbH, 4... | Camphor   | 11032035            | 1       |
| Caelo                      | Camphor   | 11032035            | 3       |
| Sanacorp                   | Camphor   | 11032035            | 1       |
| sanacorp                   | Camphor   | 11074501            | 1       |
| Caelo                      | Camphor   | 11286905            | 5       |
| Caelo                      | Camphor   | 11286909            | 2       |
| Caelo                      | Camphor   | 11286910            | 1       |
| Fagron                     | Camphor   | 11H30-N15           | 2       |
| Fagron                     | Camphor   | 11K23-N04           | 1       |
| Euro OTC                   | Camphor   | 1202021             | 1       |
| Noweda                     | Camphor   | 1202021-01          | 1       |
| Euro OTC                   | Camphor   | 1202021-01          | 4       |
| Anzag ek:8.85EUR 23.08.12  | Camphor   | 1202021-01          | 1       |
| Euro OTC                   | Camphor   | 1202021-02          | 1       |
| Anzag 17.06.2013           | Camphor   | 1202021-02          | 1       |
| Phönix                     | Camphor   | 1202021-02          | 1       |
| Caelo                      | Camphor   | 12054105            | 1       |
| Caelo                      | Camphor   | 12054107            | 5       |
| Caelo                      | Camphor   | 12054113            | 1       |
| Caelo                      | Camphor   | 12054114            | 2       |
| Caelo                      | Camphor   | 12054124            | 3       |
| Caelo                      | Camphor   | 12054141            | 6       |
| Caelo                      | Camphor   | 12054142            | 6       |
| Caelo                      | Camphor   | 12054143            | 1       |
| Caelo                      | Camphor   | 12054149            | 6       |
| Sanacorp                   | Camphor   | 12054149            | 1       |
| Caedo                      | Camphor   | 12054149            | 1       |
| Caelo                      | Camphor   | 12054151            | 2       |
| Caelo                      | Camphor   | 120564113           | 1       |
| Caelo                      | Camphor   | 12061411            | 1       |
| Euro OTC                   | Camphor   | 1210030-01          | 9       |
| EuRho                      | Camphor   | 1210030-01          | 2       |
| Euro OTC                   | Camphor   | 121003001           | 1       |
| Gehe                       | Camphor   | 1210030-01          | 1       |
| Euro OTC                   | Camphor   | 1210030-02          | 4       |
| Caelo                      | Camphor   | 1210030-02          | 1       |

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| Supplier                   | Substance | Batch            | Spectra |
|----------------------------|-----------|------------------|---------|
| Großhandel                 | Camphor   | 1210030-02       | 1       |
| Caelo                      | Camphor   | 12228205         | 1       |
| Caelo                      | Camphor   | 12228206         | 1       |
| Caelo                      | Camphor   | 12243701         | 1       |
| Caelo                      | Camphor   | 12344905         | 6       |
|                            | Camphor   | 12344909         | 1       |
| Fagron                     | Camphor   | 12B14-N09        | 1       |
| Fagron                     | Camphor   | 12D23-N03        | 2       |
| Fagron                     | Camphor   | 12G02-N09        | 3       |
| Euro OTC                   | Camphor   | 1303013-01       | 6       |
| Bombastus                  | Camphor   | 1303013-01       | 1       |
| Euro OTC                   | Camphor   | 1303013-02       | 9       |
| euroct/gehe                | Camphor   | 1303013-02       | 1       |
| Großhandel                 | Camphor   | 1303013-02       | 2       |
| EuRho                      | Camphor   | 1303013-02       | 2       |
| Euro OTC                   | Camphor   | 130313-02        | 1       |
| Caelo                      | Camphor   | 1309019-03       | 1       |
| Euro OTC                   | Camphor   | 1309019-02       | 1       |
| Caelo                      | Camphor   | 13108106         | 2       |
| Caelo                      | Camphor   | 13108110         | 1       |
| Caelo                      | Camphor   | 13108114         | 2       |
| Caelo/ Noweda              | Camphor   | 13108116         | 1       |
| Caelo                      | Camphor   | 13108118         | 1       |
| Caelo                      | Camphor   | 13195301         | 3       |
| Caelo                      | Camphor   | 13195314         | 7       |
| Caelo                      | Camphor   | 13195316         | 5       |
| Caelo                      | Camphor   | 13195318         | 1       |
| Caelo                      | Camphor   | 13195320         | 2       |
| Caelo                      | Camphor   | 13195322         | 7       |
| Caelo                      | Camphor   | 13195326         | 3       |
| Caelo                      | Camphor   | 13195328         | 1       |
| Caelo                      | Camphor   | 13205501         | 2       |
| Caelo                      | Camphor   | 13205502         | 1       |
| Caelo                      | Camphor   | 13205508         | 1       |
| Caelo                      | Camphor   | 13205511         | 3       |
| Caelo                      | Camphor   | 13205512         | 2       |
| Caelo                      | Camphor   | 13205522         | 4       |
| Cae                        | Camphor   | 13205512         | 1       |
| Caelo                      | Camphor   | 13205518         | 1       |
| Caelo                      | Camphor   | 13205517         | 1       |
| Fagron                     | Camphor   | 13H23-B04-288376 | 1       |
| Fagron                     | Camphor   | 13H23-B40-291888 | 1       |
| Fagron                     | Camphor   | 13H23-B40-294116 | 1       |
| Fagron                     | Camphor   | 13h23-b40-294116 | 1       |
| Fagron                     | Camphor   | 13H23-B40-296252 | 1       |
| Fagron                     | Camphor   | 13K28-B04        | 2       |
| Phönix                     | Camphor   | 13K28-B04        | 1       |
| Fagron                     | Camphor   | 13K28-B04-289340 | 1       |
| Fagron                     | Camphor   | 13K28-B04-294937 | 1       |
| Camphor & Allied Produc... | Camphor   | 1406029-01       | 1       |
| Euro OTC                   | Camphor   | 1406029-02       | 1       |
| Euro OTC                   | Camphor   | 1412023-01       | 1       |
| Caelo                      | Camphor   | 1412023-01       | 2       |
| Caelo                      | Camphor   | 14202801         | 1       |
| phönix                     | Camphor   | 14202801         | 1       |
| Phönix Gotha               | Camphor   | 14202801         | 1       |
| Caelo                      | Camphor   | 14202807         | 2       |
| Caelo                      | Camphor   | 14224302         | 1       |
| Caelo                      | Camphor   | 14224303         | 4       |
| Sanacorp                   | Camphor   | 14224303         | 1       |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------|------------------|----------------|
| Caelo                      | Camphor          | 14224304         | 1              |
| Caelo                      | Camphor          | 14310109         | 1              |
| Caelo                      | Camphor          | 14310705         | 11             |
| Caelo                      | Camphor          | 14310703         | 1              |
| Caelo                      | Camphor          | 14310709         | 3              |
| Sanacorp                   | Camphor          | 14310709         | 1              |
| Caelo                      | Camphor          | 14310713         | 1              |
| Caelo                      | Camphor          | 14310715         | 1              |
| Caelo                      | Camphor          | 14310718         | 1              |
| Caesar&Loretz              | Camphor          | 14310719         | 1              |
| Sanacorp                   | Camphor          | 14310720         | 2              |
| Caelo                      | Camphor          | 1480             | 2              |
| Fagron                     | Camphor          | 14G23-B04        | 2              |
| Fagron                     | Camphor          | 14G23-B04-296868 | 1              |
| Fagron                     | Camphor          | 14G23-B04-299202 | 2              |
| Fagron                     | Camphor          | 14G23-B04-301878 | 1              |
| Fagron                     | Camphor          | 14G23-B04-301879 | 1              |
| Caelo                      | Camphor          |                  | 2              |
| Fagron                     | Camphor          | 15/18-B11-321658 | 1              |
| Caelo                      | Camphor          | 15062702         | 4              |
| Caelo                      | Camphor          | 15086801         | 1              |
| Calo/AHD                   | Camphor          | 15086803         | 1              |
| Caelo                      | Camphor          | 15086806         | 1              |
| Fagron                     | Camphor          | 15097801         | 1              |
| Caelo                      | Camphor          | 15097803         | 2              |
| Caelo                      | Camphor          | 15120901         | 2              |
| Caelo                      | Camphor          | 15120902         | 1              |
| Caelo                      | Camphor          | 15316801         | 2              |
| Caesar & Loretz GmbH Hi... | Camphor          | 15316801         | 1              |
| Caelo                      | Camphor          | 15316806         | 2              |
| Caelo                      | Camphor          | 15316807         | 4              |
| Phoenix                    | Camphor          | 15316811         | 1              |
| Caelo                      | Camphor          | 15316811         | 4              |
| Caelo                      | Camphor          | 15316812         | 1              |
| Caelo                      | Camphor          | 15316815         | 3              |
| Caelo                      | Camphor          | 15316819         | 2              |
| Caelo                      | Camphor          | 15320604         | 3              |
| Caelo                      | Camphor          | 15397704         | 3              |
| Caelo                      | Camphor          | 16209301         | 3              |
| Camphor & Allied Produc... | Camphor          | 16209302         | 1              |
| Gehe                       | Camphor          | 16209305         | 1              |
| Caelo                      | Camphor          | 16235404         | 1              |
| Phoenix                    | Camphor          | 16235405         | 1              |
| Fagron                     | Camphor          | 16E23-B08        | 1              |
| Caelo                      | Camphor          | 17004301         | 2              |
| Caelo                      | Camphor          | 17004302         | 1              |
| Caelo                      | Camphor          | 2344905          | 1              |
| EuRho                      | Camphor          | 2111E-01219      | 1              |
| Galke                      | Camphor          | 23624            | 1              |
| Caelo                      | Camphor          | 25041401         | 1              |
| Euro OTC                   | Camphor          | 2803020-01       | 2              |
| Caelo                      | Camphor          | 2811Q-01221      | 1              |
| Caelo                      | Camphor          | 5315I-01221      | 1              |
| Fagron                     | Camphor          | 690442           | 1              |
| AHD, 30.10.2013            | Camphor          | 747564           | 1              |
| Euro OTC                   | Camphor          | 821509           | 1              |
| Fagron                     | Camphor          | 825653           | 1              |
| Klenk                      | Camphor          | 444A150721       | 2              |
| Caelo                      | Camphor          | 914E-01221       | 1              |
| Gehe                       | Camphor          | 10L08-N06        | 1              |

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| Supplier      | Substance | Batch          | Spectra |
|---------------|-----------|----------------|---------|
| Euro OTC      | Camphor   | 1101029-02     | 1       |
| Euro OTC      | Camphor   | 1106007-02     | 1       |
| Caelo         | Camphor   | 1202021-01     | 2       |
| GEHE          | Camphor   | 12K17-N09      | 1       |
| Fagron        | Camphor   | 1309019-02     | 1       |
| Caelo         | Camphor   | 13195304       | 1       |
| Caelo         | Camphor   | 13195311       | 2       |
| Caelo         | Camphor   | 13195323       | 1       |
| Fagron        | Camphor   | 13K28B04294933 | 1       |
| Caelo         | Camphor   | 4444A150721    | 1       |
| Caelo         | Camphor   | 444A100826     | 1       |
| Caelo         | Camphor   | 11032023       | 1       |
| Caelo         | Camphor   | 444A140526     | 1       |
| Caelo         | Camphor   | 11032025       | 1       |
| Caelo         | Camphor   | 11074509       | 1       |
| Caelo         | Camphor   | 1210030-01     | 1       |
| Caesar/Noweda | Camphor   | 13195328       | 1       |
| Caelo         | Camphor   | 16209305       | 1       |

- 69 292 spectra from 414 *Apo-Ident* customers from a total of 23 642 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Camphor* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Camphor* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 284           | 6              | 146 439       |
| <b>Type C</b> | 0              | 306           | 35             | 69 292        |

The substance/substance group *Camphor* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 97.9310 % (> 96.8966 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 89.7361 % (> 88.8563 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21599     | 23065               | 8.53                         | 48.96                           |
| 22256     | 23310               | 17.55                        | 45.76                           |
| 22279     | 23065               | 5.12                         | 47.99                           |
| 23065     | 23065               | 0.00                         | 49.65                           |
| 23310     | 23310               | 0.00                         | 46.98                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Cannabidiol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22416-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Cannabidiol

### Special notes

When selecting the *Cannabidiol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cannabidiol*:

| Supplier        | Substance   | Batch         | Sample ID | Spectra | Certificate |
|-----------------|-------------|---------------|-----------|---------|-------------|
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22412     | 40      | 1316Q-07806 |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22416     | 40      | 1316Q-07806 |
| THC-Pharma GmbH | Cannabidiol | CBD-API17-003 | 23398     | 40      | 20170609    |
| THC-Pharma GmbH | Cannabidiol | CBD-API16-003 | 23464     | 40      | 2017B-03911 |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22412SI   | 40      | 1316Q-07806 |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22416SI   | 40      | 1316Q-07806 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Cannabidiol*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 671 spectra of 16 reference samples from the substance/substance group *Cannabidiol*.

| Supplier        | Substance   | Batch         | Sample ID            | Spectra |
|-----------------|-------------|---------------|----------------------|---------|
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22412 <sup>†</sup>   | 20      |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22413                | 60      |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22414                | 60      |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22415                | 60      |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22416 <sup>†</sup>   | 20      |
| THC-Pharma GmbH | Cannabidiol | CBD-API17-003 | 23399                | 40      |
| THC-Pharma GmbH | Cannabidiol | CBD-API16-004 | 23465                | 40      |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22412SI <sup>†</sup> | 20      |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22413SI              | 60      |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22414SI              | 60      |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22415SI              | 60      |
| THC-Pharma GmbH | Cannabidiol | 15-7221-80338 | 22416SI <sup>†</sup> | 20      |
| THC-Pharma GmbH | Cannabidiol | CBD-API17-003 | 23398SI              | 40      |
| THC-Pharma GmbH | Cannabidiol | CBD-API17-003 | 23399SI              | 31      |
| THC-Pharma GmbH | Cannabidiol | CBD-API16-003 | 23464SI              | 40      |
| THC-Pharma GmbH | Cannabidiol | CBD-API16-004 | 23465SI              | 40      |

- 146 058 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 26 spectra from 3 *Apo-Ident* customers from 11 batches from the substance/substance group *Cannabidiol*.

| Supplier                   | Substance   | Batch         | Spectra |
|----------------------------|-------------|---------------|---------|
| THC-Pharm                  | Cannabidiol |               | 12      |
| Caelo                      | Cannabidiol | 110216-02     | 3       |
| THC-Pharm                  | Cannabidiol | CBDAP/17-003  | 3       |
| THC-Pharm                  | Cannabidiol | cbd-adi17-002 | 1       |
| THC Pharm GmbH             | Cannabidiol | CBD-API16-001 | 2       |
| THC Pharm                  | Cannabidiol | CBD-API16-004 | 1       |
| Fagron                     | Cannabidiol | CBD-API17-002 | 1       |
| THC-Pharm                  | Cannabidiol | CBD-API17-004 | 1       |
| THC Pharm GmbH / THC Ph... | Cannabidiol | CBD-API17-005 | 1       |
| THC-Pharm                  | Cannabidiol | CBD-API17-005 | 1       |

- 69 607 spectra from 414 *Apo-Ident* customers from a total of 23 790 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cannabidiol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cannabidiol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 670           | 1              | 146 058       |
| <b>Type C</b> | 0              | 25            | 1              | 69 607        |

The substance/substance group *Cannabidiol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.8510 % (> 99.4039 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 96.1538 % (> 84.6154 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22412     | 22412               | 0.00                         | 81.70                           |
| 22416     | 22416               | 0.00                         | 82.55                           |
| 23398     | 22412               | 9.80                         | 81.87                           |
| 23464     | 23464               | 0.00                         | 81.04                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Capsaicin, natural**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20854-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Capsaicin, natural; Capsaicinoida

### Special notes

When selecting the *Capsaicin, natural* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Capsaicin, natural*:

| Supplier | Substance          | Batch      | Sample ID | Spectra | Certificate        |
|----------|--------------------|------------|-----------|---------|--------------------|
| Fagron   | Capsaicin, natural | 13D12-N01  | 20854     | 40      | 1411392            |
| Fagron   | Capsaicin, natural | 13J07-N07  | 21340     | 40      | AR-15-FG-007151-01 |
| Euro OTC | Capsaicin, natural | 118066-04  | 21638     | 40      | 20140227           |
| Euro OTC | Capsaicin, natural | 1603005-01 | 22930     | 40      | 20160401           |
| Euro OTC | Capsaicin, natural | 1703023    | 23145     | 40      | 20170407*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Capsaicin, natural*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 70 spectra of 3 reference samples from the substance/substance group *Capsaicin, natural*.

| Supplier | Substance          | Batch      | Sample ID          | Spectra |
|----------|--------------------|------------|--------------------|---------|
| Euro OTC | Capsaicin, natural | 118066-04  | 21638 <sup>†</sup> | 20      |
| Euro OTC | Capsaicin, natural | 1603005-01 | 22931              | 40      |
| Euro OTC | Capsaicin, natural | 1603005-01 | not required       | 10      |

- 146 659 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 2 spectra from 2 *Apo-Ident* customers from 1 batches from the substance/substance group *Capsaicin, natural*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance          | Batch      | Spectra |
|----------|--------------------|------------|---------|
| Euro OTC | Capsaicin, natural | 1401043-02 | 2       |

- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Capsaicin, natural* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Capsaicin, natural* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 70            | 0              | 146 659       |
| <b>Type C</b> | 0              | 2             | 0              | 69 631        |

The substance/substance group *Capsaicin, natural* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 91.4286 %) |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20854     | 20854               | 0.00                         | 17.16                           |
| 21340     | 21340               | 0.00                         | 18.17                           |
| 21638     | 21340               | 9.40                         | 22.46                           |
| 22930     | 23145               | 2.74                         | 16.18                           |
| 23145     | 23145               | 0.00                         | 16.55                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Captopril**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20890-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Captopril; Captoprilum

### Special notes

When selecting the *Captopril* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Captopril*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------|------------------|-----------|---------|--------------------|
| Fagron   | Captopril | 12G25-N08        | 20890     | 40      | 20120814           |
| Caelo    | Captopril | 12339610         | 21064     | 40      | 1403227            |
| Caelo    | Captopril | 15189502         | 21874     | 40      | AR-15-FG-014855-01 |
| Fagron   | Captopril | 14B26-B01-312221 | 21921     | 40      | 20140317           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Captopril*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 340 spectra of 9 reference samples from the substance/substance group *Captopril*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Fagron   | Captopril | 10L09-N17        | 20255              | 30      |
| Caelo    | Captopril | 15189502         | 21874 <sup>†</sup> | 20      |
| Fagron   | Captopril | 14B26-B01-312221 | 21921 <sup>†</sup> | 20      |
| Caelo    | Captopril | 170772           | 23366              | 40      |
| Fagron   | Captopril | 17G21-B02-337989 | 23588              | 30      |
| Caelo    | Captopril | 172102           | 23676              | 40      |
| Caelo    | Captopril | 15189502         | 21874SI            | 60      |
| Fagron   | Captopril | 14B26-B01-312221 | 21921SI            | 60      |
| Caelo    | Captopril | 170772           | 23366SI            | 40      |

- 146 389 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 138 spectra from 48 *Apo-Ident* customers from 57 batches from the substance/substance group *Captopril*.

| Supplier                 | Substance | Batch            | Spectra |
|--------------------------|-----------|------------------|---------|
| Fagron                   | Captopril | 80616-6          | 1       |
| Caelo                    | Captopril | 12339616         | 2       |
| Caelo                    | Captopril | 12339602         | 1       |
| Caelo                    | Captopril | 12339604         | 2       |
| Caelo                    | Captopril | 12339605         | 4       |
| Caelo                    | Captopril | 12339606         | 1       |
| Caelo                    | Captopril | 12339607         | 1       |
| Herstellung              | Captopril | 12339607         | 1       |
| AHD, 24.09.2013          | Captopril | 12339608         | 1       |
| Caelo                    | Captopril | 12339611         | 2       |
| Caelo                    | Captopril | 12339610         | 2       |
| Caelo/Sanacorp           | Captopril | 12339617         | 1       |
| Caelo                    | Captopril | 12339618         | 1       |
| Caelo                    | Captopril | 12339619         | 1       |
| Caelo                    | Captopril | 12F29-N04        | 1       |
| Fagron                   | Captopril | 12G25-N08        | 11      |
| Fagron                   | Captopril | 12J09-N09        | 1       |
| Fagron                   | Captopril | 12K-16N04        | 1       |
| Fagron                   | Captopril | 12K16-N04        | 1       |
| Caelo                    | Captopril | 14196901         | 1       |
| Caelo                    | Captopril | 14196902         | 1       |
| Fagron                   | Captopril | 14196902         | 1       |
| Caelo                    | Captopril | 14196903         | 2       |
| Caelo                    | Captopril | 14196904         | 7       |
| Caelo                    | Captopril | 14196905         | 4       |
| Caelo                    | Captopril | 14196906         | 1       |
| Phonix                   | Captopril | 14B26-B01        | 1       |
| Fagron                   | Captopril | 14B26-B01        | 6       |
| Fagron                   | Captopril | 14B26B01         | 1       |
| Fagron                   | Captopril | 14B26-B012911557 | 1       |
| Fagron                   | Captopril | 14B26-B01-291555 | 4       |
| Caelo                    | Captopril | 14B26-B01-291555 | 1       |
| Fagron                   | Captopril | 14B26-B01-291556 | 1       |
| Fagron                   | Captopril | 14B26-B01-291557 | 6       |
| Sonnenberg-Apotheke      | Captopril | 14B26-B01-291557 | 2       |
| Caelo                    | Captopril | 14B26-B01-291557 | 1       |
| Fagron                   | Captopril | 14B26-B01-302337 | 1       |
| Fagron                   | Captopril | 14B26-B01-302338 | 2       |
| Fagron                   | Captopril | 14B26-B01-310127 | 1       |
| Fagron                   | Captopril | 14B26-B01-310127 | 2       |
| Caelo                    | Captopril | 14B26-B01-310127 | 1       |
| Fagron                   | Captopril | 14B26-B01-314460 | 1       |
| Hedinger                 | Captopril | 14B26-B40        | 2       |
| Fagron                   | Captopril | 14B26-B40-318894 | 5       |
| Fagron/Sanacorp          | Captopril | 14B26-B40-318894 | 1       |
| Fagron                   | Captopril | 14B26-B40-320183 | 3       |
| Fagron                   | Captopril | 14B26-B40-321319 | 3       |
| Changzhou Pharmaceutical | Captopril | 14B26-B40-321319 | 1       |
| Caelo                    | Captopril | 14B26-B40-323267 | 1       |
| Fagron                   | Captopril | 14B26-B40-323267 | 2       |
| Fagron                   | Captopril | 14B26-B40-325275 | 1       |
| Caelo                    | Captopril | 14B26-B40-325275 | 2       |
| Caelo                    | Captopril | 14B26-B01-310127 | 1       |
| Fagron                   | Captopril | 14B26-W0129-1557 | 1       |
| Caelo                    | Captopril | 15189501         | 2       |
| Caelo                    | Captopril | 15189502         | 2       |

*continued on the next page*

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| Supplier | Substance | Batch            | Spectra |
|----------|-----------|------------------|---------|
| Euro OTC | Captopril | 15189507         | 3       |
| Caelo    | Captopril | 15189510         | 1       |
| Caelo    | Captopril | 15189509         | 1       |
| Caelo    | Captopril | 15189511         | 4       |
| Caelo    | Captopril | 15189512         | 1       |
| Caelo    | Captopril | 15189514         | 4       |
| Caelo    | Captopril | 15189517         | 1       |
| Caelo    | Captopril | 15189521         | 2       |
| Caelo    | Captopril | 15189525         | 1       |
| Caelo    | Captopril | 17077202         | 2       |
| Caelo    | Captopril | 5102-14-042      | 1       |
| Fagron   | Captopril | EC140101         | 3       |
| Fagron   | Captopril | 14b26-B01-291555 | 1       |
| Caelo    | Captopril | 14B26-B40        | 1       |

- 69 495 spectra from 414 *Apo-Ident* customers from a total of 23 745 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Captopril* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Captopril* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 240           | 100            | 146 389       |
| <b>Type C</b> | 0              | 125           | 13             | 69 495        |

The substance/substance group *Captopril* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 70.5882 % (> 69.7059 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 90.5797 % (> 88.4058 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20890     | 21064               | 5.92                         | 44.38                           |
| 21064     | 21064               | 0.00                         | 46.47                           |
| 21874     | 21874               | 0.00                         | 54.81                           |
| 21921     | 21874               | 12.48                        | 51.94                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Carbomers 35000 / 50000**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20548-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Carbomers 35000 / 50000

### Special notes

When selecting the *Carbomers 35000 / 50000* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Carbomers 35000 / 50000*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Caelo    | Carbomers 35000 ... | 13135601   | 20978     | 40      | 1403767     |
| Caelo    | Carbomers 35000 ... | 13186207   | 20979     | 40      | 1403768     |
| Caelo    | Carbomers 35000 ... | 14057902   | 21354     | 40      | 20140228    |
| Euro OTC | Carbomers 35000 ... | 1311027-02 | 21561     | 40      | 20131205    |
| Euro OTC | Carbomers 35000 ... | 1512010    | 22250     | 40      | 20151216*   |

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| Supplier | Substance           | Batch   | Sample ID | Spectra | Certificate |
|----------|---------------------|---------|-----------|---------|-------------|
| Euro OTC | Carbomers 35000 ... | 1604032 | 22548     | 40      | 20160428*   |
| Euro OTC | Carbomers 35000 ... | 1607028 | 22686     | 40      | 20160804*   |
| Caelo    | Carbomers 35000 ... | 162530  | 22759     | 40      | 20161011*   |
| Euro OTC | Carbomers 35000 ... | 1610024 | 22852     | 40      | 20161102*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 360 spectra of 9 reference samples from the substance/substance group *Carbomers 35000 / 50000*. These samples are listed above in the [calibration samples](#) section.
- 71 026 spectra from a total of 1543 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 340 spectra of 9 reference samples from the substance/substance group *Carbomers 35000 / 50000*.

| Supplier | Substance               | Batch      | Sample ID          | Spectra |
|----------|-------------------------|------------|--------------------|---------|
| Caelo    | Carbomers 35000 / 50000 | 11351507   | 20548              | 40      |
| Caelo    | Carbomers 35000 / 50000 | 11351604   | 20550              | 40      |
| Caelo    | Carbomers 35000 / 50000 | 11351611   | 20561              | 40      |
| Caelo    | Carbomers 35000 / 50000 | 14057903   | 21557              | 60      |
| Euro OTC | Carbomers 35000 / 50000 | 1311027-02 | 21561 <sup>†</sup> | 20      |
| Euro OTC | Carbomers 35000 / 50000 | 1512010    | 22250 <sup>†</sup> | 20      |
| Euro OTC | Carbomers 35000 / 50000 | 1702012    | 23139              | 40      |
| Euro OTC | Carbomers 35000 / 50000 | 1706015    | 23534              | 40      |
| Caelo    | Carbomers 35000 / 50000 | 172520     | 23621              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 146389 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 236 spectra from 139 *Apo-Ident* customers from 78 batches from the substance/substance group *Carbomers 35000 / 50000*.

| Supplier           | Substance               | Batch       | Spectra |
|--------------------|-------------------------|-------------|---------|
| Euro OTC           | Carbomers 35000 / 50000 | 101616773   | 1       |
| Euro OTC           | Carbomers 35000 / 50000 | 12052014A   | 1       |
| Caelo              | Carbomers 35000 / 50000 | 12274907    | 8       |
| Euro OTC           | Carbomers 35000 / 50000 | 1305007-01  | 2       |
| Euro OTC           | Carbomers 35000 / 50000 | 130800601   | 1       |
| Euro OTC           | Carbomers 35000 / 50000 | 1311027-01  | 3       |
| Euro OTC           | Carbomers 35000 / 50000 | 1311027-02  | 5       |
| Caelo              | Carbomers 35000 / 50000 | 1311027-02  | 1       |
| Caelo              | Carbomers 35000 / 50000 | 13194501    | 6       |
| Caelo              | Carbomers 35000 / 50000 | 14016208    | 7       |
| Caelo              | Carbomers 35000 / 50000 | 13194503    | 8       |
| Caelo              | Carbomers 35000 / 50000 | 14016209    | 3       |
| Caelo              | Carbomers 35000 / 50000 | 14057903    | 2       |
| Euro OTC           | Carbomers 35000 / 50000 | 1410001-01  | 11      |
| Euro OTC           | Carbomers 35000 / 50000 | 141000101   | 1       |
| EuRho              | Carbomers 35000 / 50000 | 1410001-01  | 1       |
| Fischer/Gehe       | Carbomers 35000 / 50000 | 1410001-02  | 1       |
| Caelo              | Carbomers 35000 / 50000 | 1410001-02  | 1       |
| Sanacorp           | Carbomers 35000 / 50000 | 14149911    | 1       |
| Caelo              | Carbomers 35000 / 50000 | 15015703    | 2       |
| Caelo              | Carbomers 35000 / 50000 | 15101801    | 3       |
| Caelo              | Carbomers 35000 / 50000 | 15101802    | 6       |
| Euro OTC           | Carbomers 35000 / 50000 | 1512010-01  | 4       |
| Alliance H.        | Carbomers 35000 / 50000 | 1512010-01  | 1       |
| Euro OTC           | Carbomers 35000 / 50000 | 1512010-02  | 2       |
| Caelo              | Carbomers 35000 / 50000 | 15439002    | 3       |
| Caelo              | Carbomers 35000 / 50000 | 15439003    | 9       |
| Euro OTC           | Carbomers 35000 / 50000 | 1604032-01  | 2       |
| Euro OTC           | Carbomers 35000 / 50000 | 1607028-01  | 2       |
| Euro/Phönix        | Carbomers 35000 / 50000 | 161002401   | 1       |
| Gehe               | Carbomers 35000 / 50000 | 16237501    | 1       |
| Caelo              | Carbomers 35000 / 50000 | 16253004    | 3       |
| Caelo              | Carbomers 35000 / 50000 | 16253009    | 4       |
| Caelo              | Carbomers 35000 / 50000 | 2215M-01232 | 1       |
| Euro OTC           | Carbomers 35000 / 50000 | 4311027-01  | 1       |
| Phoenix            | Carbomers 35000 / 50000 | 1305007-01  | 1       |
| Caelo              | Carbomers 35000 / 50000 | 1308006-01  | 1       |
| Sanacorp           | Carbomers 35000 / 50000 | 1311027-01  | 1       |
| Caelo              | Carbomers 35000 / 50000 | 13186207    | 4       |
| Phoenix            | Carbomers 35000 / 50000 | 13194505    | 1       |
| Caelo              | Carbomers 35000 / 50000 | 13194507    | 5       |
| Sanacorp           | Carbomers 35000 / 50000 | 6/AKD13     | 1       |
| Euro OTC           | Carbomers 35000 / 50000 | 101217279   | 1       |
| Caelo              | Carbomers 35000 / 50000 | 11351604    | 2       |
| Phoenix 25.07.2012 | Carbomers 35000 / 50000 | 11351605    | 1       |

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| Supplier                   | Substance               | Batch      | Spectra |
|----------------------------|-------------------------|------------|---------|
| Caelo                      | Carbomers 35000 / 50000 | 11351605   | 2       |
| Caelo                      | Carbomers 35000 / 50000 | 11351618   | 4       |
| Euro OTC                   | Carbomers 35000 / 50000 | 1202020-01 | 2       |
| Euro OTC                   | Carbomers 35000 / 50000 | 1210037-01 | 7       |
| EuRho                      | Carbomers 35000 / 50000 | 1210037-01 | 1       |
| Gehe 01.07.2013            | Carbomers 35000 / 50000 | 12274908   | 2       |
| Caelo                      | Carbomers 35000 / 50000 | 12274910   | 3       |
| Caelo                      | Carbomers 35000 / 50000 | 12274912   | 5       |
| Caelo                      | Carbomers 35000 / 50000 | 12274916   | 11      |
| Caelo                      | Carbomers 35000 / 50000 | 12274922   | 1       |
| Euro/Sanacorp              | Carbomers 35000 / 50000 | 1305007-01 | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 13186205   | 6       |
| GEHE                       | Carbomers 35000 / 50000 | 11351616   | 1       |
| Euro OTC                   | Carbomers 35000 / 50000 | 141000-01  | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 14149910   | 2       |
| Caelo                      | Carbomers 35000 / 50000 | 14310806   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 15015709   | 2       |
| Caelo                      | Carbomers 35000 / 50000 | 15101807   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 15101809   | 3       |
| Caesar & Loretz GmbH Hi... | Carbomers 35000 / 50000 | 15101809   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 15101810   | 4       |
| Caelo                      | Carbomers 35000 / 50000 | 1510801    | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 15257401   | 1       |
| Caesar&Loretz,Phönix,06... | Carbomers 35000 / 50000 | 15439003   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 16253005   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 12274908   | 5       |
| Caelo                      | Carbomers 35000 / 50000 | 13186203   | 3       |
| Caelo                      | Carbomers 35000 / 50000 | 13194512   | 1       |
| Phoenix 16.04.2014         | Carbomers 35000 / 50000 | 13194503   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 14057902   | 1       |
| Ichthyol/Phönix            | Carbomers 35000 / 50000 | 14149905   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 14149904   | 1       |
| Sanacaorp                  | Carbomers 35000 / 50000 | 14149905   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 14149905   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 14149906   | 2       |
| Caelo                      | Carbomers 35000 / 50000 | 14149911   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 15015702   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 11013605   | 2       |
| Fagron                     | Carbomers 35000 / 50000 | 13194503   | 1       |
| Gehe                       | Carbomers 35000 / 50000 | 13194505   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 13194505   | 2       |
| Caelo                      | Carbomers 35000 / 50000 | 13194511   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 10157812   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 11013613   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 11307511   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 11351601   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 11351616   | 1       |
| Erika apotheke             | Carbomers 35000 / 50000 | 11351618   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 11351623   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 12274914   | 4       |
| Hepart AG                  | Carbomers 35000 / 50000 | 12274916   | 1       |
| Sanacorp                   | Carbomers 35000 / 50000 | 12274922   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 13186201   | 2       |
| Caelo                      | Carbomers 35000 / 50000 | 28111310   | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 2913M1232  | 1       |
| Caelo                      | Carbomers 35000 / 50000 | 31631293   | 1       |

- 69 397 spectra from 414 *Apo-Ident* customers from a total of 23 724 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Carbomers 35000 / 50000* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Carbomers 35000 / 50000* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 360           | 0              | 71 026        |
| <b>Type B</b> | 0              | 340           | 0              | 146 389       |
| <b>Type C</b> | 0              | 226           | 10             | 69 397        |

The substance/substance group *Carbomers 35000 / 50000* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.3333 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.2353 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 95.7627 % (> 94.4915 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20978     | 20978               | 0.00                         | 44.67                           |
| 20979     | 20979               | 0.00                         | 43.09                           |
| 21354     | 22250               | 7.64                         | 37.77                           |
| 21561     | 22686               | 5.65                         | 37.63                           |
| 22250     | 22250               | 0.00                         | 39.71                           |
| 22548     | 22548               | 0.00                         | 38.38                           |
| 22686     | 22686               | 0.00                         | 39.20                           |
| 22759     | 22759               | 0.00                         | 25.46                           |
| 22852     | 22852               | 0.00                         | 41.06                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | Carmellose sodium (400/450/500/600/1600/2000 mPa · s)           |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20866-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Carmellose sodium (400/450/500/600/1600/2000 mPa · s); Carmellosum natricum (400/450/500/600/1600/2000 mPa · s); Natrii carboxymethylcellulosi (400/450/500/600/1600/2000 mPa · s)

### Special notes

When selecting the *Carmellose sodium (400/450/500/600/1600/2000 mPa · s)* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Carmellose sodium (400/450/500/600/1600/2000 mPa · s)*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------------|-----------|-----------|---------|-------------|
| Caelo    | Carmellose sodiu... | 12354404  | 20866     | 40      | 1401185     |
| Caelo    | Carmellose sodiu... | 13104807  | 20872     | 40      | 1401186     |
| Fagron   | Carmellose sodiu... | 13D22-N02 | 20892     | 40      | 1401187     |
| Caelo    | Carmellose sodiu... | 14029211  | 21382     | 40      | 20140127    |

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| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate        |
|----------|---------------------|----------|-----------|---------|--------------------|
| Caelo    | Carmellose sodiu... | 13299310 | 21432     | 40      | 20131002           |
| Caelo    | Carmellose sodiu... | 161714   | 22645     | 40      | 20160713*          |
| Caelo    | Carmellose sodiu... | 16171406 | 23187     | 40      | AR-17-FG-015964-01 |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 280 spectra of 7 reference samples from the substance/substance group *Carmellose sodium* (400/450/500/600/1600/2000 mPa · s). These samples are listed above in the [calibration samples](#) section.
- 71 106 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Carmellose sodium* (400/450/500/600/1600/2000 mPa · s).

| Supplier    | Substance                       | Batch    | Sample ID          | Spectra |
|-------------|---------------------------------|----------|--------------------|---------|
| zu erfassen | Carmellose sodium (400/450/5... | pending  | 20144              | 40      |
| zu erfassen | Carmellose sodium (400/450/5... | pending  | 20147              | 40      |
| Caelo       | Carmellose sodium (400/450/5... | 13299310 | 21432 <sup>†</sup> | 20      |
| Caelo       | Carmellose sodium (400/450/5... | 17062304 | 23519              | 40      |
| Caelo       | Carmellose sodium (400/450/5... | 172446   | 23623              | 40      |

- 146 549 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B*

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 43 spectra from 20 *Apo-Ident* customers from 30 batches from the substance/substance group *Carmellose sodium* (400/450/500/600/1600/2000 mPa · s).

| Supplier           | Substance                       | Batch            | Spectra |
|--------------------|---------------------------------|------------------|---------|
| Caelo              | Carmellose sodium (400/450/5... | 12354416         | 3       |
| Caelo              | Carmellose sodium (400/450/5... | 11124211         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 11124212         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 13104810         | 2       |
| Bombastus          | Carmellose sodium (400/450/5... | 13104813         | 3       |
| Phönix             | Carmellose sodium (400/450/5... | 12354416         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 1315Q-03302      | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 13299302         | 2       |
| Gehe 06.10.14      | Carmellose sodium (400/450/5... | 13299312         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 13G19-N02        | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 14029201         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 14149806         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 15123901         | 3       |
| Caelo              | Carmellose sodium (400/450/5... | 15123908         | 2       |
| Fagron             | Carmellose sodium (400/450/5... | 15G03-Bo2-312862 | 1       |
|                    | Carmellose sodium (400/450/5... | 28051402         | 1       |
| Noweda             | Carmellose sodium (400/450/5... | 12354401         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 13104802         | 2       |
| Caelo              | Carmellose sodium (400/450/5... | 913M-03302       | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 11124218         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 12079615         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 12079618         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 12255708         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 12354408         | 3       |
| Fagron             | Carmellose sodium (400/450/5... | 13D22-N02        | 1       |
| Anzag/             | Carmellose sodium (400/450/5... | 21733            | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 12354403         | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 14029211         | 1       |
| Gutenberg-Apotheke | Carmellose sodium (400/450/5... | 4811E-03302      | 1       |
| Sanacorp           | Carmellose sodium (400/450/5... | AKD6             | 1       |
| Caelo              | Carmellose sodium (400/450/5... | 12354418         | 1       |

- 69 590 spectra from 414 *Apo-Ident* customers from a total of 23 773 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Carmellose sodium* (400/450/500/600/1600/2000 mPa · s) can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Carmellose sodium* (400/450/500/600/1600/2000 mPa · s) and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct



and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 280           | 0              | 71 106        |
| Type B | 0              | 167           | 13             | 146 549       |
| Type C | 0              | 36            | 7              | 69 590        |

The substance/substance group *Carmellose sodium* (400/450/500/600/1600/2000 mPa · s) can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.8571 %) |
| Type B | 100.0000 % (> 99.9923 %) | 92.7778 % (> 91.1111 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 83.7209 % (> 76.7442 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20866     | 20866               | 0.00                         | 53.02                           |
| 20872     | 20872               | 0.00                         | 57.42                           |
| 20892     | 20892               | 0.00                         | 56.64                           |
| 21382     | 20872               | 8.32                         | 54.59                           |
| 21432     | 20866               | 12.83                        | 50.68                           |
| 22645     | 22645               | 0.00                         | 48.30                           |
| 23187     | 23187               | 0.00                         | 48.93                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Cellulose, microcrystalline**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20708-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Cellulose, microcrystalline; Cellulosum microcristallinum; Cellulosum microcrystallinum

### Special notes

When selecting the *Cellulose, microcrystalline* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cellulose, microcrystalline*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Cellulose, micro... | 12C23-N06        | 20708     | 70      | 1403080     |
| Euro OTC | Cellulose, micro... | 1201004-01       | 20728     | 40      | 20120201    |
| Euro OTC | Cellulose, micro... | 1211037-01       | 21080     | 40      | 20121207    |
| Euro OTC | Cellulose, micro... | 1507022          | 21857     | 40      | 20150805*   |
| Euro OTC | Cellulose, micro... | 1604029          | 22559     | 40      | 20160512*   |
| Fagron   | Cellulose, micro... | 16B24-B11-323324 | 22896     | 40      | 20160311    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 270 spectra of 6 reference samples from the substance/substance group *Cellulose, microcrystalline*. These samples are listed above in the [calibration samples](#) section.
- 71 116 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Cellulose, microcrystalline*.

| Supplier | Substance                   | Batch      | Sample ID          | Spectra |
|----------|-----------------------------|------------|--------------------|---------|
| Euro OTC | Cellulose, microcrystalline | 1211037-01 | 21085              | 40      |
| Euro OTC | Cellulose, microcrystalline | 1507022    | 21857 <sup>†</sup> | 20      |
| Euro OTC | Cellulose, microcrystalline | 1607042    | 22794              | 40      |
| Euro OTC | Cellulose, microcrystalline | 1604029-01 | 22815              | 40      |
| Euro OTC | Cellulose, microcrystalline | 1610030    | 22876              | 40      |

- 146 549 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 32 spectra from 23 *Apo-Ident* customers from 18 batches from the substance/substance group *Cellulose, microcrystalline*.

| Supplier   | Substance                   | Batch            | Spectra |
|------------|-----------------------------|------------------|---------|
| Euro OTC   | Cellulose, microcrystalline | 1211037-01       | 3       |
| Euro OTC   | Cellulose, microcrystalline | 1309001-01       | 3       |
| Euro OTC   | Cellulose, microcrystalline | 1309001-02       | 2       |
| Euro OTC   | Cellulose, microcrystalline | 135010001        | 1       |
| Euro OTC   | Cellulose, microcrystalline | 1410002-01       | 4       |
| Euro OTC   | Cellulose, microcrystalline | 150702201        | 1       |
| Fagron     | Cellulose, microcrystalline | 15C03-B06-305242 | 1       |
| Euro OTC   | Cellulose, microcrystalline | 1604029-01       | 2       |
| Euro OTC   | Cellulose, microcrystalline | 1610030-01       | 1       |
| Fagron     | Cellulose, microcrystalline | 16B24-B11        | 1       |
| Fagron     | Cellulose, microcrystalline | 17A11-B04-331463 | 1       |
| Euro OTC   | Cellulose, microcrystalline | 700204           | 1       |
| Fagron     | Cellulose, microcrystalline | 9K10-N10         | 1       |
| Fagron     | Cellulose, microcrystalline | 2013M-01350      | 1       |
| Euro OTC   | Cellulose, microcrystalline | 1201004-02       | 2       |
| EuRho      | Cellulose, microcrystalline | 1201004-02       | 1       |
| Euro OTC   | Cellulose, microcrystalline | 121103701        | 1       |
| Phnoix     | Cellulose, microcrystalline | 1211037-01       | 1       |
| Phoenix    | Cellulose, microcrystalline | 1309001-02       | 1       |
| Fagron     | Cellulose, microcrystalline | 13A03-N01        | 1       |
| Koisser    | Cellulose, microcrystalline | E0790            | 1       |
| apo-ident. | Cellulose, microcrystalline | 1604029-01       | 1       |

- 69 601 spectra from 414 *Apo-Ident* customers from a total of 23 783 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cellulose, microcrystalline* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cellulose, microcrystalline* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 270           | 0              | 71 116        |
| <b>Type B</b> | 0              | 180           | 0              | 146 549       |
| <b>Type C</b> | 0              | 31            | 1              | 69 601        |

The substance/substance group *Cellulose, microcrystalline* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.7778 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.6667 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 96.8750 % (> 87.5000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20708     | 20708               | 0.00                         | 56.45                           |
| 20728     | 20708               | 3.13                         | 56.24                           |
| 21080     | 21857               | 7.18                         | 52.59                           |
| 21857     | 21857               | 0.00                         | 56.15                           |
| 22559     | 22559               | 0.00                         | 68.00                           |
| 22896     | 21857               | 2.92                         | 55.13                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Cetostearyl alcohol</b>                                      |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20738-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Cetostearyl alcohol; Alcohol cetylicus; Alcohol cetylicus et stearylicus; Alcohol cetylicus et stearylicus emulsificans A; Alcohol cetylstearylicus; Alcohol cetylstearylicus emulsificans A; Cetyl alcohol; Emulgade® 1000 NI; Emulsifying cetostearyl alcohol (type A)

### Special notes

When selecting the *Cetostearyl alcohol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cetostearyl alcohol*:

| Supplier | Substance                     | Batch     | Sample ID | Spectra | Certificate |
|----------|-------------------------------|-----------|-----------|---------|-------------|
| Fagron   | Emulgade <sup>®</sup> 1000 NI | 12H07-N06 | 20738     | 30      | 20120905    |
| Caelo    | Cetyl alcohol                 | 13096901  | 20896     | 40      | 1405179     |
| Fagron   | Cetostearyl alco...           | 13C13-N13 | 20968     | 40      | 1402265     |

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| Supplier | Substance                     | Batch            | Sample ID | Spectra | Certificate        |
|----------|-------------------------------|------------------|-----------|---------|--------------------|
| Fagron   | Emulgade <sup>®</sup> 1000 NI | 13C05-B40-289262 | 21054     | 40      | 1408003            |
| Fagron   | Emulsifying ceto...           | 13L17-B05        | 21279     | 40      | 1505070            |
| Caelo    | Cetostearyl alco...           | 14054504         | 21314     | 40      | 20140226           |
| Caelo    | Emulsifying ceto...           | 13233005         | 21319     | 30      | 1506057            |
| Caelo    | Emulgade <sup>®</sup> 1000 NI | 14055001         | 21381     | 40      | 20140225           |
| Caelo    | Cetyl alcohol                 | 13286502         | 21435     | 40      | 20130925           |
| Caelo    | Emulsifying ceto...           | 14322505         | 21830     | 40      | 20141031           |
| Euro OTC | Emulsifying ceto...           | 1510043          | 21998     | 40      | 20151124*          |
| Euro OTC | Emulsifying ceto...           | 1504010-01       | 22264     | 40      | 20150423           |
| Caelo    | Cetyl alcohol                 | 15323301         | 22266     | 40      | AR-16-FG-008835-01 |
| Caelo    | Emulsifying ceto...           | 153857           | 22332     | 40      | 20151202*          |
| Caelo    | Emulsifying ceto...           | 153856           | 22334     | 40      | 20160210*          |
| Caelo    | Emulgade <sup>®</sup> 1000 NI | 15277504         | 22390     | 40      | 20150828           |
| Caelo    | Emulgade <sup>®</sup> 1000 NI | 160804           | 22397     | 40      | 20160323*          |
| Caelo    | Cetyl alcohol                 | 161063           | 22398     | 40      | 20160420*          |
| Caelo    | Cetyl alcohol                 | 161063           | 22403     | 40      | 20160420*          |
| Euro OTC | Cetyl alcohol                 | 1508014-01       | 22611     | 40      | 20150821           |
| Fagron   | Emulsifying ceto...           | 16I13-B01-326511 | 23022     | 40      | 20161024           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 820 spectra of 21 reference samples from the substance/substance group *Cetostearyl alcohol*. These samples are listed above in the [calibration samples](#) section.
- 70 566 spectra from a total of 1532 batches from further 371 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 1200 spectra of 32 reference samples from the substance/substance group *Cetostearyl alcohol*.

| Supplier | Substance                       | Batch    | Sample ID | Spectra |
|----------|---------------------------------|----------|-----------|---------|
| Caelo    | Cetostearyl alcohol             | 82753089 | 20113     | 60      |
| Caelo    | Emulsifying cetostearyl alco... | 10040502 | 20163     | 40      |

continued on the next page

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

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| Supplier | Substance                       | Batch      | Sample ID          | Spectra |
|----------|---------------------------------|------------|--------------------|---------|
| Caelo    | Cetyl alcohol                   | 10144209   | 20283              | 30      |
| Caelo    | Emulsifying cetostearyl alco... | 11L22-N09  | 20513              | 40      |
| Fagron   | Cetostearyl alcohol             | 12C21-N09  | 20555              | 40      |
| Fagron   | Emulsifying cetostearyl alco... | 12C30-N01  | 20586              | 40      |
| Fagron   | Emulsifying cetostearyl alco... | 11291113   | 20636              | 40      |
| Fagron   | Emulgade® 1000 NI               | 12H07-N06  | 20738 <sup>†</sup> | 10      |
| Caelo    | Cetyl alcohol                   | 13286502   | 21318              | 40      |
| Caelo    | Emulsifying cetostearyl alco... | 13233005   | 21434              | 60      |
| Caelo    | Cetyl alcohol                   | 13286502   | 21435 <sup>†</sup> | 20      |
| Caelo    | Cetostearyl alcohol             | 14054504   | 21442              | 60      |
| Caelo    | Emulsifying cetostearyl alco... | 14322505   | 21830 <sup>†</sup> | 20      |
| Euro OTC | Emulsifying cetostearyl alco... | 1510043    | 21998 <sup>†</sup> | 20      |
| Euro OTC | Emulsifying cetostearyl alco... | 1504010-01 | 22264 <sup>†</sup> | 20      |
| Caelo    | Cetyl alcohol                   | 15323301   | 22266 <sup>†</sup> | 20      |
| Caelo    | Emulsifying cetostearyl alco... | 153857     | 22331              | 60      |
| Caelo    | Emulsifying cetostearyl alco... | 153857     | 22332 <sup>†</sup> | 20      |
| Caelo    | Emulsifying cetostearyl alco... | 153856     | 22333              | 60      |
| Caelo    | Emulsifying cetostearyl alco... | 153856     | 22334 <sup>†</sup> | 20      |
| Caelo    | Emulgade® 1000 NI               | 160804     | 22395              | 40      |
| Caelo    | Emulgade® 1000 NI               | 160804     | 22396              | 40      |
| Caelo    | Cetyl alcohol                   | 161063     | 22399              | 40      |
| Caelo    | Cetyl alcohol                   | 161063     | 22400              | 40      |
| Caelo    | Cetyl alcohol                   | 161063     | 22401              | 40      |
| Caelo    | Cetyl alcohol                   | 161063     | 22402              | 40      |
| Euro OTC | Emulsifying cetostearyl alco... | 1604013    | 22540              | 40      |
| Euro OTC | Emulsifying cetostearyl alco... | 1701031    | 22999              | 40      |
| Caelo    | Cetyl alcohol                   | 170473     | 23068              | 40      |
| Caelo    | Cetostearyl alcohol             | 170492     | 23097              | 40      |
| Euro OTC | Emulsifying cetostearyl alco... | 1705001    | 23381              | 40      |
| Caelo    | Emulsifying cetostearyl alco... | 171980     | 23575              | 40      |

- 145 529 spectra from a total of 3169 batches from further 859 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 516 spectra from 189 *Apo-Ident* customers from 188 batches from the substance/substance group *Cetostearyl alcohol*.

| Supplier | Substance                       | Batch     | Spectra |
|----------|---------------------------------|-----------|---------|
| Fagron   | Emulsifying cetostearyl alco... | 12L19-N03 | 8       |
| Caelo    | Emulsifying cetostearyl alco... | 13233008  | 2       |
| Caelo    | Cetyl alcohol                   | 13286502  | 6       |
| Caelo    | Emulsifying cetostearyl alco... | 13352102  | 1       |
| Fagron   | Emulsifying cetostearyl alco... | 13F07-N05 | 10      |

continued on the next page

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



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| <b>Supplier</b>        | <b>Substance</b>                | <b>Batch</b>     | <b>Spectra</b> |
|------------------------|---------------------------------|------------------|----------------|
| Fagron                 | Emulsifying cetostearyl alco... | 13L17-B05        | 2              |
| Fagron                 | Emulsifying cetostearyl alco... | 13L17-B05-289805 | 6              |
| Caelo                  | Emulsifying cetostearyl alco... | 14158201         | 9              |
| Caelo                  | Emulsifying cetostearyl alco... | 14322505         | 9              |
| Caelo                  | Cetostearyl alcohol             | 14346201         | 4              |
| Fagron                 | Cetostearyl alcohol             | 14G31-B03        | 1              |
| Sanacorp               | Emulsifying cetostearyl alco... | 15090701         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 15090706         | 2              |
| Caelo                  | Emulsifying cetostearyl alco... | 15271402         | 9              |
| Euro OTC               | Emulsifying cetostearyl alco... | 15271403         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 15271405         | 8              |
| Fagron                 | Emulsifying cetostearyl alco... | 15C31-B99-307062 | 3              |
| Fagron                 | Cetostearyl alcohol             | 3414E-01078      | 1              |
| Caelo                  | Cetyl alcohol                   | P134/14          | 1              |
| Caelo                  | Cetyl alcohol                   | 13210504         | 12             |
| Fagron                 | Cetostearyl alcohol             | 12C30-N01        | 3              |
| Fagron                 | Cetostearyl alcohol             | 7886542          | 1              |
| Fagron                 | Emulsifying cetostearyl alco... | 9652865          | 2              |
| Caelo                  | Emulsifying cetostearyl alco... | 12331402         | 6              |
| Fagron                 | Emulsifying cetostearyl alco... | 12G02-N04        | 6              |
| Sanacorp               | Emulsifying cetostearyl alco... | 12J29-N04        | 1              |
| Fagron                 | Emulsifying cetostearyl alco... | 12J29-N04        | 4              |
| A.H.D.                 | Emulsifying cetostearyl alco... | 12L19-N03        | 2              |
| Caelo                  | Emulsifying cetostearyl alco... | 13144105         | 10             |
| Caelo                  | Emulsifying cetostearyl alco... | 13233002         | 2              |
| Caelo                  | Cetyl alcohol                   | 12271103         | 6              |
| Caelo                  | Cetyl alcohol                   | 13096901         | 6              |
| Euro OTC               | Cetyl alcohol                   | 13286502         | 1              |
| Caelo                  | Cetyl alcohol                   | 14141501         | 1              |
| Caelo                  | Cetyl alcohol                   | 14262204         | 7              |
| Caelo                  | Cetyl alcohol                   | 14349101         | 12             |
| Caelo                  | Cetyl alcohol                   | 15323301         | 4              |
| Caelo                  | Cetyl alcohol                   | 1523316          | 1              |
| Caelo                  | Cetyl alcohol                   | 15323311         | 5              |
| Caelo                  | Cetyl alcohol                   | 16106307         | 2              |
| Caelo                  | Cetyl alcohol                   | 16335802         | 1              |
| Caelo                  | Cetyl alcohol                   | 16335807         | 1              |
| Caelo                  | Cetyl alcohol                   | 1112013B         | 1              |
| Finze                  | Cetyl alcohol                   | 10321703         | 1              |
| EuRho Anzag ek:3,47EUR | Cetyl alcohol                   | 110505501        | 1              |
| Euro OTC               | Cetyl alcohol                   | 1105055-01       | 1              |
| Caelo                  | Cetyl alcohol                   | 11153405         | 1              |
| Caelo                  | Cetyl alcohol                   | 11153416         | 1              |
| Caelo                  | Cetyl alcohol                   | 11320702         | 3              |
| Caelo                  | Cetyl alcohol                   | 12018605         | 2              |
| EuRho                  | Cetyl alcohol                   | 1206020-01       | 1              |
| Euro OTC               | Cetyl alcohol                   | 1206020-01       | 1              |
| Euro OTC               | Cetyl alcohol                   | 1211002-01       | 3              |
| Caelo                  | Cetyl alcohol                   | 12338604         | 6              |
| Fagron                 | Cetyl alcohol                   | 12A-02N12        | 1              |
| Phönix                 | Cetyl alcohol                   | 13096901         | 1              |
| Caelo                  | Cetyl alcohol                   | 13096904         | 2              |
| Phonix                 | Cetyl alcohol                   | 13210504         | 1              |
| Sanacorpaelo /Sanacorp | Cetyl alcohol                   | 1AKS11           | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 12065709         | 7              |
| Caelo                  | Cetyl alcohol                   | 20250112-1       | 1              |
| Caelo                  | Cetostearyl alcohol             | 13018305         | 7              |
| Euro OTC               | Cetostearyl alcohol             | 130503501        | 1              |
| Berkel AHK             | Cetostearyl alcohol             | 13144105         | 1              |
| Caelo                  | Cetostearyl alcohol             | 13144105         | 2              |

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| <b>Supplier</b>            | <b>Substance</b>    | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|---------------------|------------------|----------------|
| Caelo                      | Cetostearyl alcohol | 13206206         | 4              |
| ahd/lamotte                | Cetostearyl alcohol | 13210504         | 1              |
| Fagron                     | Cetostearyl alcohol | 13F07-N05        | 2              |
| Fagron                     | Cetostearyl alcohol | 13L17-B05        | 1              |
| Fagron                     | Cetostearyl alcohol | 13L17-B05-289805 | 2              |
| Fagron                     | Cetostearyl alcohol | 13L17-B05-289806 | 3              |
| Euro OTC                   | Cetostearyl alcohol | 1404019-01       | 2              |
| Fagron                     | Cetostearyl alcohol | 13L17-B05-294999 | 1              |
| Euro OTC                   | Cetostearyl alcohol | 1404019-02       | 1              |
| Caelo                      | Cetostearyl alcohol | 14054504         | 4              |
| Gehe                       | Cetostearyl alcohol | 14054504         | 1              |
| Caelo                      | Cetostearyl alcohol | 14054508         | 3              |
| Caelo                      | Cetostearyl alcohol | 14158201         | 4              |
| Berkel AHK                 | Cetostearyl alcohol | 14158201         | 2              |
| Caelo                      | Cetostearyl alcohol | 14215007         | 7              |
| Phoenix                    | Cetostearyl alcohol | 14322505         | 2              |
| Caelo                      | Cetostearyl alcohol | 14322506         | 1              |
| Fagron                     | Cetostearyl alcohol | 14G31-B03-297611 | 1              |
| Euro OTC                   | Cetostearyl alcohol | 150401001        | 1              |
| Caelo                      | Cetostearyl alcohol | 15090701         | 2              |
| Euro OTC                   | Cetostearyl alcohol | 1504010-01       | 1              |
| Caelo                      | Cetostearyl alcohol | 15271405         | 2              |
| Caelo                      | Cetostearyl alcohol | 15272702         | 2              |
| Caesar/Noweda              | Cetostearyl alcohol | 15272705         | 1              |
| Caelo                      | Cetostearyl alcohol | 15272717         | 2              |
| Caelo                      | Cetostearyl alcohol | 15272709         | 4              |
| Fagron                     | Cetostearyl alcohol | 15D24-B02-308261 | 2              |
| Caelo                      | Cetostearyl alcohol | 16119604         | 1              |
| Ebert-Jacobi               | Cetostearyl alcohol | 16230603         | 1              |
| Fagron                     | Cetostearyl alcohol | 16B23-B07-318218 | 1              |
| Bombastus                  | Cetostearyl alcohol | 295148           | 1              |
| Bombastus                  | Cetostearyl alcohol | 300132           | 2              |
| Sanacorp                   | Cetostearyl alcohol | 575778           | 1              |
| Fagron                     | Cetostearyl alcohol | 8256792          | 3              |
| Fagron                     | Cetostearyl alcohol | 9652865          | 1              |
| Fagron                     | Cetostearyl alcohol | 10F17-N02        | 1              |
| Euro OTC                   | Cetostearyl alcohol | 1107035-01       | 1              |
| Caelo                      | Cetostearyl alcohol | 11302101         | 2              |
| Caesar & Loretz GmbH, 4... | Cetostearyl alcohol | 11302101         | 1              |
| Fagron                     | Cetostearyl alcohol | 11E17-N13        | 1              |
| Fagron                     | Cetostearyl alcohol | 11f30-n11        | 1              |
| Fagron                     | Cetostearyl alcohol | 11K17-N02        | 1              |
| Caelo                      | Cetostearyl alcohol | 11K17-N02        | 1              |
| Fagron                     | Cetostearyl alcohol | 12/17-N05        | 1              |
| Caelo                      | Cetostearyl alcohol | 12021304         | 1              |
| Caelo                      | Cetostearyl alcohol | 12025301         | 2              |
| Euro OTC                   | Cetostearyl alcohol | 1204015-01       | 1              |
| Caelo                      | Cetostearyl alcohol | 12065705         | 1              |
| Caelo                      | Cetostearyl alcohol | 12065709         | 1              |
| Euro OTC                   | Cetostearyl alcohol | 1212019-01       | 1              |
| Fagron                     | Cetostearyl alcohol | 12E30-N13        | 1              |
| Fagron                     | Cetostearyl alcohol | 12g02-n04        | 1              |
| Fagron                     | Cetostearyl alcohol | 12G02-N04        | 9              |
| Fagron                     | Cetostearyl alcohol | 12J17-N05        | 3              |
| Fagron                     | Cetostearyl alcohol | 12J17-N05        | 1              |
| Fagron                     | Cetostearyl alcohol | 12J29-N04        | 1              |
| Fagron                     | Cetostearyl alcohol | 12K22-N03        | 3              |
| Fagron                     | Cetostearyl alcohol | 12L19-N03        | 1              |
| Caelo                      | Cetostearyl alcohol | 13018306         | 1              |
| Euro OTC                   | Cetostearyl alcohol | 1305035-01       | 1              |

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| <b>Supplier</b>            | <b>Substance</b>                | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|---------------------------------|------------------|----------------|
| Caelo                      | Cetostearyl alcohol             | 1314405          | 1              |
| Fagron                     | Cetostearyl alcohol             | 13C13-N13        | 1              |
| Caelo                      | Cetostearyl alcohol             | 14061317         | 1              |
| Euro OTC                   | Cetostearyl alcohol             | 20270912-2       | 1              |
| Caesar/Noweda              | Cetostearyl alcohol             | 2911E-01077      | 2              |
| Caelo                      | Emulgade® 1000 NI               | 15113703         | 1              |
| AHD                        | Emulgade® 1000 NI               | 8073743          | 1              |
| Caelo                      | Emulgade® 1000 NI               | 14055002         | 1              |
| Caelo                      | Emulgade® 1000 NI               | 13092401         | 1              |
| Caelo                      | Emulgade® 1000 NI               |                  | 1              |
| Caelo                      | Emulgade® 1000 NI               | 12032002         | 1              |
| Euro OTC                   | Emulsifying cetostearyl alco... | 10836573         | 1              |
| Caelo                      | Emulsifying cetostearyl alco... | 5011505          | 1              |
| Caelo                      | Emulsifying cetostearyl alco... | 9170717          | 1              |
| Caelo                      | Emulsifying cetostearyl alco... | 13233005         | 9              |
| Caelo                      | Emulsifying cetostearyl alco... | 13233006         | 1              |
| Caesar & Loretz GmbH       | Emulsifying cetostearyl alco... | 13233008         | 1              |
| Sanacorp                   | Emulsifying cetostearyl alco... | 13F07-N05        | 1              |
| PHOENIX am07.04.2014       | Emulsifying cetostearyl alco... | 13F07-N05        | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 13I06-N04        | 1              |
| Alliance Health 24.07.2... | Emulsifying cetostearyl alco... | 13L17-B05-289805 | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 13L17B05289805   | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 13L17-B05-289806 | 3              |
| Fagron                     | Emulsifying cetostearyl alco... | 13L17-B05-294999 | 3              |
| Caelo                      | Emulsifying cetostearyl alco... | 13L17-B05-289806 | 1              |
| Euro OTC                   | Emulsifying cetostearyl alco... | 1404019-01       | 1              |
| Caelo                      | Emulsifying cetostearyl alco... | 14156201         | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 14G31-B03        | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 14G31-B03-297610 | 3              |
| alliance health. 05.05...  | Emulsifying cetostearyl alco... | 14G31-B03-297610 | 1              |
| Euro OTC                   | Emulsifying cetostearyl alco... | 14G31-B03-297610 | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 14G31-B03-305612 | 2              |
| Euro OTC                   | Emulsifying cetostearyl alco... | 150410-01        | 1              |
| Caelo                      | Emulsifying cetostearyl alco... | 15090701         | 7              |
| Caelo                      | Emulsifying cetostearyl alco... | 15090703         | 3              |
| Euro OTC                   | Emulsifying cetostearyl alco... | 1510043-01       | 1              |
| Caesar&Loretz/Noweda       | Emulsifying cetostearyl alco... | 15271405         | 1              |
| Sanacorp                   | Emulsifying cetostearyl alco... | 15271405         | 1              |
| Caelo                      | Emulsifying cetostearyl alco... | 15271407         | 3              |
| Caelo                      | Emulsifying cetostearyl alco... | 15271408         | 2              |
| Caelo                      | Emulsifying cetostearyl alco... | 15385602         | 3              |
| Caelo                      | Emulsifying cetostearyl alco... | 15385606         | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 15C31-B00-307062 | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 15D24-B02        | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 15D24-B02-308261 | 2              |
| Fagron                     | Emulsifying cetostearyl alco... | 15D24-B02-311993 | 6              |
| Euro OTC                   | Emulsifying cetostearyl alco... | 1604013-02       | 1              |
| Caelo                      | Emulsifying cetostearyl alco... | 16119604         | 4              |
| Caelo                      | Emulsifying cetostearyl alco... | 16238607         | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 16B23-B07-318218 | 1              |
| Fagron                     | Emulsifying cetostearyl alco... | 16B23-B07-320384 | 2              |
| Fagron                     | Emulsifying cetostearyl alco... | 16B23-B07-323025 | 1              |
| Gehe                       | Emulsifying cetostearyl alco... | 1701031-01       | 1              |
| Caelo                      | Emulsifying cetostearyl alco... | 17056802         | 1              |
| Caelo                      | Emulsifying cetostearyl alco... | 17056806         | 1              |
| Caelo                      | Emulsifying cetostearyl alco... | 23051503         | 1              |
| Caelo                      | Emulsifying cetostearyl alco... |                  | 1              |
| Bombastus                  | Emulsifying cetostearyl alco... | 288691           | 3              |
| Bombastus                  | Emulsifying cetostearyl alco... | 295148           | 1              |
| Bombastus                  | Emulsifying cetostearyl alco... | 300132           | 2              |

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| <b>Supplier</b>        | <b>Substance</b>                | <b>Batch</b>     | <b>Spectra</b> |
|------------------------|---------------------------------|------------------|----------------|
| Henry Lamotte / Noweda | Emulsifying cetostearyl alco... | 300132           | 1              |
| Bombastus              | Emulsifying cetostearyl alco... | 303935           | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 303935           | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 31032015B        | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 608/10072017     | 1              |
| Fagron                 | Emulsifying cetostearyl alco... | 8256792          | 2              |
| GEHE                   | Emulsifying cetostearyl alco... | 8440094          | 1              |
| Fagron                 | Emulsifying cetostearyl alco... | 14175700         | 1              |
| Euro OTC               | Emulsifying cetostearyl alco... | 1003050-01       | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 11291103         | 2              |
| Fagron                 | Emulsifying cetostearyl alco... | 11L22-N09        | 1              |
| Caesar & Loretz GmbH   | Emulsifying cetostearyl alco... | 12065703         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 12331407         | 3              |
| Fagron                 | Emulsifying cetostearyl alco... | 12602-N04        | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 12C30-N01        | 1              |
| Fagron                 | Emulsifying cetostearyl alco... | 12G02N04         | 1              |
| Anzag                  | Emulsifying cetostearyl alco... | 12G02-N04        | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 13144104         | 3              |
| Noweda                 | Emulsifying cetostearyl alco... | 13144104         | 1              |
| Phönix                 | Emulsifying cetostearyl alco... | 1323305          | 1              |
| Sanacorp               | Emulsifying cetostearyl alco... | 13I06-N04        | 1              |
| Caesar&lorenz,Phoenix  | Emulsifying cetostearyl alco... | 14158201         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 14G31-B03-305612 | 3              |
| Euro OTC               | Emulsifying cetostearyl alco... | 15271410         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 15271403         | 4              |
| Fagron                 | Emulsifying cetostearyl alco... | 20260712-2       | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 25/AKD1          | 1              |
| Bombastus              | Emulsifying cetostearyl alco... | 278418           | 1              |
| Noweda                 | Emulsifying cetostearyl alco... | 13065576         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 13144103         | 1              |
| Euro OTC               | Emulsifying cetostearyl alco... | 1404019-02       | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 14322512         | 1              |
| Euroh/Noweda           | Emulsifying cetostearyl alco... | 1504010-01       | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 15271410         | 1              |
| Phönix                 | Emulsifying cetostearyl alco... | 15C31-B99-307062 | 1              |
| Fagron                 | Emulsifying cetostearyl alco... | 2215I-01078      | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 23091402         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 19032014B        | 1              |
| Fagron                 | Emulsifying cetostearyl alco... | 3013M-01078      | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | Unbekannt        | 1              |
| Caelo                  | Cetyl alcohol                   | 1212E-01076      | 1              |
| Fagron                 | Emulsifying cetostearyl alco... | 11499002         | 1              |
| Bombastus              | Emulsifying cetostearyl alco... | 265360           | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 2011404          | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 11009204         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 11291104         | 1              |
| Caesar/Noweda          | Emulsifying cetostearyl alco... | 11343405         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 11291101         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 12065703         | 1              |
| Noweda                 | Emulsifying cetostearyl alco... | 12065705         | 1              |
| Caesar/Noweda          | Emulsifying cetostearyl alco... | 12065707         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 12134203         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 12229402         | 2              |
| Caelo                  | Emulsifying cetostearyl alco... | 12231402         | 1              |
| Euro OTC               | Emulsifying cetostearyl alco... | 1305035-01       | 2              |
| Phoenix 26.11.12       | Emulsifying cetostearyl alco... | 13144105         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 13233001         | 1              |
| Caesar/Lorenz          | Emulsifying cetostearyl alco... | 13233005         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 18081201         | 1              |
| Caelo                  | Emulsifying cetostearyl alco... | 21121-01078      | 1              |

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| Supplier | Substance                       | Batch       | Spectra |
|----------|---------------------------------|-------------|---------|
| Caelo    | Emulsifying cetostearyl alco... | 24101305    | 1       |
| Caelo    | Emulsifying cetostearyl alco... | 25051201    | 1       |
| Fagro    | Emulsifying cetostearyl alco... | 5211Q-01078 | 1       |
| Caelo    | Cetostearyl alcohol             | 11162305    | 1       |
| Sanacorp | Cetostearyl alcohol             | 13206206    | 1       |

- 69 117 spectra from 414 *Apo-Ident* customers from a total of 23 616 batches from a further 693 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cetostearyl alcohol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cetostearyl alcohol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 820           | 0              | 70 566        |
| <b>Type B</b> | 0              | 1177          | 23             | 145 529       |
| <b>Type C</b> | 0              | 492           | 24             | 69 117        |

The substance/substance group *Cetostearyl alcohol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 99.2683 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 98.0833 % (> 97.8333 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 95.3488 % (> 94.7674 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20738     | 21054               | 4.11                         | 51.19                           |
| 20896     | 20896               | 0.00                         | 44.97                           |
| 20968     | 20968               | 0.00                         | 47.00                           |
| 21054     | 21054               | 0.00                         | 44.05                           |
| 21279     | 21279               | 0.00                         | 50.63                           |
| 21314     | 21998               | 10.01                        | 46.62                           |
| 21319     | 21319               | 0.00                         | 52.53                           |
| 21381     | 22397               | 6.33                         | 53.56                           |
| 21435     | 20896               | 21.06                        | 44.31                           |
| 21830     | 21998               | 1.65                         | 51.90                           |
| 21998     | 21998               | 0.00                         | 51.47                           |
| 22264     | 22334               | 1.31                         | 49.93                           |
| 22266     | 22266               | 0.00                         | 43.31                           |
| 22332     | 22332               | 0.00                         | 49.07                           |
| 22334     | 22334               | 0.00                         | 50.04                           |
| 22390     | 21054               | 6.03                         | 55.28                           |
| 22397     | 22397               | 0.00                         | 36.61                           |
| 22398     | 22398               | 0.00                         | 44.00                           |
| 22403     | 22403               | 0.00                         | 45.04                           |
| 22611     | 22398               | 22.82                        | 43.42                           |
| 23022     | 22334               | 2.46                         | 50.61                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Chloral hydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20322-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Chloral hydrate; Chlorali hydras; Chloralum hydratum

### Special notes

When selecting the *Chloral hydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Chloral hydrate*:

| Supplier | Substance       | Batch     | Sample ID | Spectra | Certificate |
|----------|-----------------|-----------|-----------|---------|-------------|
| Fagron   | Chloral hydrate | 13F06-N07 | 21231     | 40      | 20130626    |
| Caelo    | Chloral hydrate | 13213311  | 21309     | 40      | 20130712    |
| Caelo    | Chloral hydrate | 15448318  | 22963     | 40      | 1704462     |
| Caelo    | Chloral hydrate | 16355802  | 23094     | 40      | 20170112    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Chloral hydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 6 reference samples from the substance/substance group *Chloral hydrate*.

| Supplier | Substance       | Batch            | Sample ID | Spectra |
|----------|-----------------|------------------|-----------|---------|
| Fagron   | Chloral hydrate | 11J05-N01        | 20322     | 40      |
| Fagron   | Chloral hydrate | 12C26-M04        | 20552     | 40      |
| Caelo    | Chloral hydrate | 154483           | 23355     | 40      |
| Fagron   | Chloral hydrate | 17E05-B05-335580 | 23572     | 40      |
| Caelo    | Chloral hydrate | 172506           | 23646     | 40      |
| Caelo    | Chloral hydrate | 172477           | 23678     | 40      |

- 146 489 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 173 spectra from 78 *Apo-Ident* customers from 75 batches from the substance/substance group *Chloral hydrate*.



| Supplier            | Substance       | Batch              | Spectra |
|---------------------|-----------------|--------------------|---------|
| Caelo               | Chloral hydrate | 3121403            | 1       |
| Fagron              | Chloral hydrate | 12H06-N080160/161  | 1       |
| Fagron              | Chloral hydrate | 12H06-N081114/1612 | 1       |
| Fagron              | Chloral hydrate | 12H06-N08          | 17      |
| Caelo               | Chloral hydrate | 13002417           | 3       |
| Caelo               | Chloral hydrate | 13002425           | 4       |
| Caelo               | Chloral hydrate | 13213311           | 1       |
| Fagron              | Chloral hydrate | 13D22-N11          | 1       |
| Fagron              | Chloral hydrate | 13F06-N07          | 4       |
| Fagron              | Chloral hydrate | 13K05-B13          | 1       |
| Caelo               | Chloral hydrate | 1403815            | 1       |
| Caelo               | Chloral hydrate | 14038301           | 4       |
| Phönix Gotha        | Chloral hydrate | 14038302           | 1       |
| Caelo               | Chloral hydrate | 14038306           | 1       |
| Caelo               | Chloral hydrate | 14038311           | 4       |
| Caelo               | Chloral hydrate | 14218701           | 2       |
| Euro OTC            | Chloral hydrate | 14218702           | 1       |
| Caelo               | Chloral hydrate | 14218704           | 3       |
| Caelo               | Chloral hydrate | 14218705           | 2       |
| Sanacorp            | Chloral hydrate | 14218705           | 1       |
| Caelo               | Chloral hydrate | 14218709           | 6       |
| Caelo               | Chloral hydrate | 14218710           | 1       |
| CAESAR-LORETZ /GEHE | Chloral hydrate | 14218710           | 1       |
| Caelo               | Chloral hydrate | 14218712           | 1       |
| Fagron              | Chloral hydrate | 14218712           | 1       |
| Caelo               | Chloral hydrate | 14218713           | 1       |
| Caelo               | Chloral hydrate | 14218714           | 4       |
| Fagron              | Chloral hydrate | 14218719           | 1       |
| Caelo               | Chloral hydrate | 14218719           | 5       |
| Caelo               | Chloral hydrate | 14218720           | 1       |
| Noweda29.04.2015    | Chloral hydrate | 15083701           | 2       |
| Caelo               | Chloral hydrate | 15083703           | 9       |
| Caelo               | Chloral hydrate | 15083704           | 1       |
| Caelo               | Chloral hydrate | 15166501           | 1       |
| Caelo               | Chloral hydrate | 15166502           | 3       |
| Caelo               | Chloral hydrate | 15166503           | 4       |
| Caelo               | Chloral hydrate | 15166505           | 4       |
| Fagron              | Chloral hydrate | 15166505           | 1       |
| Caelo               | Chloral hydrate | 15166506           | 3       |
| Caelo               | Chloral hydrate | 15166507           | 3       |
| Caelo               | Chloral hydrate | 15166508           | 2       |
| Caelo               | Chloral hydrate | 15166513           | 3       |
| Caelo               | Chloral hydrate | 15448303           | 6       |
| Caelo               | Chloral hydrate | 15448306           | 2       |
| Caelo               | Chloral hydrate | 15448307           | 1       |
| Ebert KKH 10.10.16  | Chloral hydrate | 15448308           | 1       |
| Caelo               | Chloral hydrate | 15448310           | 1       |
| Caelo               | Chloral hydrate | 15448312           | 4       |
| Caelo               | Chloral hydrate | 15448313           | 1       |
| hochhaus-Apotheke   | Chloral hydrate | 15448314           | 2       |
| Caelo               | Chloral hydrate | 15448314           | 1       |
| Caelo               | Chloral hydrate | 15448315           | 1       |
| Caelo               | Chloral hydrate | 15448318           | 3       |
| Caelo               | Chloral hydrate | 15448321           | 1       |
| Caelo               | Chloral hydrate | 15448322           | 2       |
| Fagron              | Chloral hydrate | 160609/1           | 1       |
| Caelo               | Chloral hydrate | 17121402           | 1       |
| Caelo               | Chloral hydrate | 414061             | 1       |
| FARGON              | Chloral hydrate | 10i14-n10          | 1       |
| Fagron              | Chloral hydrate | 11D13-N07          | 1       |

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| Supplier          | Substance       | Batch              | Spectra |
|-------------------|-----------------|--------------------|---------|
| Fagron            | Chloral hydrate | 11J05-N01          | 1       |
| Caelo             | Chloral hydrate | 12017503           | 1       |
| Caelo             | Chloral hydrate | 12017512           | 2       |
| Caelo             | Chloral hydrate | 12017518           | 1       |
| Fagron            | Chloral hydrate | 12C26-M04          | 2       |
| Fagron            | Chloral hydrate | 12C26-M05          | 1       |
| Phönix,02.11.2012 | Chloral hydrate | 12C26-M05          | 1       |
| Fagron            | Chloral hydrate | 12C26-M08          | 1       |
| Phönix,02.11.2012 | Chloral hydrate | 12C26-M06          | 1       |
| Fagron            | Chloral hydrate | 12H06N08           | 3       |
| Fagron            | Chloral hydrate | 12H06-N080101/1612 | 1       |
| Anzag 17.01.2013  | Chloral hydrate | 12H06-N08          | 1       |
| Sanacorp          | Chloral hydrate | 12H06-N08          | 1       |
| Gehe              | Chloral hydrate | 12H06-N08          | 1       |
| Fagron            | Chloral hydrate | 12H06-N080013/494  | 1       |
| Caelo             | Chloral hydrate | 13d22-n11          | 1       |
| Phönix Gotha      | Chloral hydrate | 13F06-N07          | 2       |
| Fargon/ Noweda    | Chloral hydrate | 13F06N07           | 1       |
| Fagron            | Chloral hydrate | 13F06-N070631/786  | 1       |
| Caelo             | Chloral hydrate | 14101307           | 1       |
| Caelo             | Chloral hydrate | 25021401           | 1       |
| FARGON            | Chloral hydrate |                    | 1       |
| GEHE              | Chloral hydrate | 21022172/4         | 1       |
| Caelo             | Chloral hydrate | 13002405           | 1       |
| Anzag             | Chloral hydrate | 12C26M04           | 1       |

- 69 460 spectra from 414 *Apo-Ident* customers from a total of 23 727 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Chloral hydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Chloral hydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 240           | 0              | 146 489       |
| <b>Type C</b> | 0              | 172           | 1              | 69 460        |

The substance/substance group *Chloral hydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 99.4220 % (> 97.6879 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21231     | 22963               | 6.89                         | 53.38                           |
| 21309     | 22963               | 3.50                         | 53.40                           |
| 22963     | 22963               | 0.00                         | 53.50                           |
| 23094     | 22963               | 5.52                         | 53.21                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Chloramphenicol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20097-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Chloramphenicol; Chloramphenicolum

### Special notes

When selecting the *Chloramphenicol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Chloramphenicol*:

| Supplier | Substance       | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------------|------------|-----------|---------|-------------|
| Fagron   | Chloramphenicol | 11F20-N05  | 20777     | 90      | 1412249     |
| Caelo    | Chloramphenicol | 11370716   | 20787     | 40      | 20120202    |
| Caelo    | Chloramphenicol | 12248507   | 20807     | 40      | 20120831    |
| Euro OTC | Chloramphenicol | 1209019-02 | 20813     | 60      | 20130408    |
| Fagron   | Chloramphenicol | 13A11-N02  | 20822     | 30      | 20130125    |

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| Supplier | Substance       | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------------|------------------|-----------|---------|-------------|
| Caelo    | Chloramphenicol | 13080924         | 21701     | 40      | 1509287     |
| Euro OTC | Chloramphenicol | 1407043-01       | 21752     | 40      | 20140903    |
| Fagron   | Chloramphenicol | 14E01-B02-308559 | 21910     | 40      | 20140513    |
| Caelo    | Chloramphenicol | 14346908         | 21988     | 40      | 20150115    |
| Euro OTC | Chloramphenicol | 1602002          | 22367     | 30      | 20160309*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 450 spectra of 10 reference samples from the substance/substance group *Chloramphenicol*. These samples are listed above in the [calibration samples](#) section.
- 70 936 spectra from a total of 1542 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 315 spectra of 10 reference samples from the substance/substance group *Chloramphenicol*.

| Supplier | Substance       | Batch            | Sample ID          | Spectra |
|----------|-----------------|------------------|--------------------|---------|
| Euro OTC | Chloramphenicol | 1209019-02       | 20815              | 60      |
| Caelo    | Chloramphenicol | 13080924         | 21701 <sup>†</sup> | 20      |
| Euro OTC | Chloramphenicol | 1407043-01       | 21752 <sup>†</sup> | 20      |
| Fagron   | Chloramphenicol | 14E01-B02-308559 | 21910 <sup>†</sup> | 20      |
| Caelo    | Chloramphenicol | 14346908         | 21988 <sup>†</sup> | 20      |
| Euro OTC | Chloramphenicol | 1602002          | 22367 <sup>†</sup> | 15      |
| Caelo    | Chloramphenicol | 15358906         | 22961              | 40      |
| Fagron   | Chloramphenicol | 16I12-B07-327124 | 22962              | 40      |
| Caelo    | Chloramphenicol | 162786           | 23353              | 40      |
| Euro OTC | Chloramphenicol | 1704021          | 23392              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 414 spectra from a total of 3184 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 782 spectra from 256 *Apo-Ident* customers from 173 batches from the substance/substance group *Chloramphenicol*.

| Supplier                   | Substance       | Batch      | Spectra |
|----------------------------|-----------------|------------|---------|
| Caelo                      | Chloramphenicol | 3081602    | 1       |
| Caelo                      | Chloramphenicol | 93323801   | 1       |
| Caelo                      | Chloramphenicol | 11370706   | 4       |
| Caelo                      | Chloramphenicol | 11370711   | 13      |
| Euro OTC                   | Chloramphenicol | 120250     | 1       |
| Caelo                      | Chloramphenicol | 1203012-02 | 1       |
| Euro OTC                   | Chloramphenicol | 1203012-02 | 14      |
| Euro OTC                   | Chloramphenicol | 1209010-02 | 4       |
| Euro OTC                   | Chloramphenicol | 1209019-02 | 12      |
| Caelo                      | Chloramphenicol | 12248520   | 8       |
| Caelo                      | Chloramphenicol | 12248524   | 9       |
| Caelo                      | Chloramphenicol | 12248525   | 5       |
| Fagron                     | Chloramphenicol | 12B13-N06  | 8       |
| Euro OTC                   | Chloramphenicol | 1302024-01 | 10      |
| Euro OTC                   | Chloramphenicol | 1302024-02 | 7       |
| Euro OTC                   | Chloramphenicol | 130801702  | 2       |
| Caesar&Loretz GmbH/Anzag   | Chloramphenicol | 1308017-01 | 1       |
| VDL                        | Chloramphenicol | 1308017-01 | 1       |
| EuRho/Phönix               | Chloramphenicol | 1308017-01 | 1       |
| Euro OTC                   | Chloramphenicol | 1308017-01 | 7       |
| Euro OTC                   | Chloramphenicol | 130801701  | 1       |
| Caelo                      | Chloramphenicol | 1308017-01 | 1       |
| euroct/gehe                | Chloramphenicol | 1308017-01 | 2       |
| PHOENIX 25.04.2014         | Chloramphenicol | 1308017-02 | 2       |
| Euro OTC                   | Chloramphenicol | 1308017-02 | 11      |
| Euro/ Sanacorp             | Chloramphenicol | 1308017-02 | 1       |
| ANZAG                      | Chloramphenicol | 1308017-02 | 1       |
| Caelo                      | Chloramphenicol | 13080303   | 1       |
| Gehe                       | Chloramphenicol | 1308017-02 | 1       |
| Caelo                      | Chloramphenicol | 13080903   | 11      |
| Caelo                      | Chloramphenicol | 13080904   | 5       |
| AHD                        | Chloramphenicol | 13080904   | 1       |
| Caelo                      | Chloramphenicol | 13080907   | 13      |
| Phönix Gotha               | Chloramphenicol | 13080907   | 1       |
| Nanjing Baijingyu Pharm... | Chloramphenicol | 13080908   | 2       |
| noweda                     | Chloramphenicol | 13080908   | 1       |
| Caelo                      | Chloramphenicol | 13080908   | 3       |
| Caelo                      | Chloramphenicol | 13080915   | 1       |
| Caelo                      | Chloramphenicol | 13080917   | 4       |
| Caelo                      | Chloramphenicol | 13080918   | 3       |
| Phönix                     | Chloramphenicol | 13080921   | 1       |
| Caelo                      | Chloramphenicol | 13080921   | 2       |
| Caelo                      | Chloramphenicol | 13080923   | 14      |
| Caelo                      | Chloramphenicol | 13080924   | 17      |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------|------------------|----------------|
| Caelo                      | Chloramphenicol  | 13080925         | 16             |
| Euro OTC                   | Chloramphenicol  | 13111410         | 1              |
| Fagron                     | Chloramphenicol  | 13A11-N02        | 8              |
| Phönix                     | Chloramphenicol  | 13A1-802         | 1              |
| Fagron                     | Chloramphenicol  | 13A31-B02        | 8              |
| Fagron                     | Chloramphenicol  | 13A31-B02286708  | 1              |
| Caelo                      | Chloramphenicol  | 13A31-B02-286708 | 3              |
| Fagron                     | Chloramphenicol  | 13A31-B02-286709 | 3              |
| Caelo                      | Chloramphenicol  | 13A31-B02-286709 | 1              |
| Gutenberg-Apotheke         | Chloramphenicol  | 13A31-B02-286710 | 1              |
| Fagron                     | Chloramphenicol  | 13A31-B02-290263 | 1              |
| Fagron                     | Chloramphenicol  | 13A31-B02-290300 | 1              |
| Euro OTC                   | Chloramphenicol  | 1407043          | 1              |
| Caelo                      | Chloramphenicol  | 140704301        | 2              |
| Euro OTC                   | Chloramphenicol  | 1407043-01       | 21             |
| Euro OTC                   | Chloramphenicol  | 140704301        | 3              |
| Northeast General          | Chloramphenicol  | 1407043-01       | 1              |
| Alliance 15.04.2015 Ek ... | Chloramphenicol  | 1407043-01       | 1              |
| Caelo                      | Chloramphenicol  | 1407043-01       | 1              |
| VDL                        | Chloramphenicol  | 140743-01        | 1              |
| Caelo                      | Chloramphenicol  | 14246917         | 1              |
| Caelo                      | Chloramphenicol  | 1434608          | 1              |
| Caelo                      | Chloramphenicol  | 14346901         | 3              |
| Noweda                     | Chloramphenicol  | 14346901         | 2              |
| Caelo                      | Chloramphenicol  | 14346903         | 1              |
| Caelo                      | Chloramphenicol  | 14346904         | 3              |
| Caelo                      | Chloramphenicol  | 14346906         | 4              |
| Caelo                      | Chloramphenicol  | 14346907         | 9              |
| Caelo                      | Chloramphenicol  | 14346908         | 6              |
| Noweda                     | Chloramphenicol  | 14346910         | 1              |
| Caelo                      | Chloramphenicol  | 14346910         | 7              |
| Caelo                      | Chloramphenicol  | 14346911         | 12             |
| Caelo                      | Chloramphenicol  | 14346912         | 2              |
| AHD                        | Chloramphenicol  | 14346912         | 1              |
| Caelo                      | Chloramphenicol  | 14346913         | 7              |
| Caelo                      | Chloramphenicol  | 14346914         | 2              |
| Caelo                      | Chloramphenicol  | 14346917         | 6              |
| Caelo                      | Chloramphenicol  | 14346918         | 11             |
| Caelo                      | Chloramphenicol  | 14346922         | 1              |
| Caelo                      | Chloramphenicol  | 14346924         | 2              |
| Fagron                     | Chloramphenicol  | 14E01-B02        | 4              |
| Fagron                     | Chloramphenicol  | 14E01-B02-296623 | 1              |
| Caelo                      | Chloramphenicol  | 14E01-B02-296623 | 1              |
| Fagron                     | Chloramphenicol  | 14E01-B02-296624 | 6              |
| Fagron                     | Chloramphenicol  | 14E01B02296624   | 1              |
| Caelo                      | Chloramphenicol  | 14E01B02296624   | 1              |
| Fagron                     | Chloramphenicol  | 14E01-B02-296625 | 1              |
| Fagron                     | Chloramphenicol  | 14E01-B02-306146 | 7              |
| Fagron                     | Chloramphenicol  | 14E01-B02-308559 | 7              |
| Caelo                      | Chloramphenicol  |                  | 1              |
| Gehe 27.06.15/euro         | Chloramphenicol  | 1502036-01       | 2              |
| Euro OTC                   | Chloramphenicol  | 1502036-01       | 19             |
| Euro OTC                   | Chloramphenicol  | 1502036          | 1              |
| Euro OTC                   | Chloramphenicol  | 150203601        | 1              |
| Euro OTG                   | Chloramphenicol  | 1502036-01       | 1              |
| EuRho / 20                 | Chloramphenicol  | 1502036-01       | 1              |
| Euro/Alliance Healthcare   | Chloramphenicol  | 1502036-01       | 1              |
| Fagron                     | Chloramphenicol  | 1502036-01       | 1              |
| EurPS                      | Chloramphenicol  | 1502036-01       | 2              |
| Caelo                      | Chloramphenicol  | 1502036-01       | 1              |

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| <b>Supplier</b>          | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|--------------------------|------------------|-------------------|----------------|
| Euro OTC                 | Chloramphenicol  | 1502036-02        | 11             |
| Caelo                    | Chloramphenicol  | 1502036-02        | 5              |
| Northeast General/Noweda | Chloramphenicol  | 1502036-02        | 1              |
| Euro OTC                 | Chloramphenicol  | 1502036-03        | 14             |
| Euro OTC                 | Chloramphenicol  | 150203603         | 1              |
| Fischer/ Noweda          | Chloramphenicol  | 1502036-03        | 1              |
| Caelo                    | Chloramphenicol  | 15358903          | 2              |
| Caelo                    | Chloramphenicol  | 15358905          | 7              |
| Phoe                     | Chloramphenicol  | 15358905          | 1              |
| Caelo                    | Chloramphenicol  | 15358906          | 8              |
| Caelo                    | Chloramphenicol  | 15358907          | 1              |
| Caelo                    | Chloramphenicol  | 15358908          | 1              |
| Caelo                    | Chloramphenicol  | 15358909          | 2              |
| Gehe                     | Chloramphenicol  | 15358909          | 1              |
| Caelo                    | Chloramphenicol  | 15358912          | 2              |
| Caelo                    | Chloramphenicol  | 15358913          | 2              |
| Fagron                   | Chloramphenicol  | 15G14-B04-322516  | 1              |
| Fagron                   | Chloramphenicol  |                   | 2              |
| Euro OTC                 | Chloramphenicol  | 1602002-01        | 15             |
| Fagron                   | Chloramphenicol  | 16/12-B07-326036  | 1              |
| Caelo                    | Chloramphenicol  | 1602002-01        | 2              |
| Euro OTC                 | Chloramphenicol  | 16020002-03       | 1              |
| Euro OTC                 | Chloramphenicol  | 1602002-02        | 6              |
| Northeast General / Gehe | Chloramphenicol  | 1602002-02        | 1              |
| Euro OTC                 | Chloramphenicol  | 1602002-03        | 10             |
| Caelo                    | Chloramphenicol  | 1602002-03        | 1              |
| Caelo                    | Chloramphenicol  | 16358909          | 1              |
| Phönix                   | Chloramphenicol  | 16i12-b07-327124  | 1              |
| Fagron                   | Chloramphenicol  | 16112-B07-326036  | 1              |
| Fagron                   | Chloramphenicol  | 2111I-01259       | 1              |
| Sanacorp                 | Chloramphenicol  | 41/AKD24          | 1              |
| Caelo                    | Chloramphenicol  | 43/AKD15          | 1              |
| Caelo                    | Chloramphenicol  | 4412Q-01259       | 1              |
| Fagron                   | Chloramphenicol  | DY00911233        | 4              |
| Euro OTC                 | Chloramphenicol  | DY130525          | 1              |
| AHDE 20.08.15            | Chloramphenicol  | DY00912128        | 1              |
| Euro OTC                 | Chloramphenicol  | DY00912128        | 3              |
| Fagron                   | Chloramphenicol  | DY00912129        | 1              |
| Caelo                    | Chloramphenicol  | DY130525          | 2              |
| Euro OTC                 | Chloramphenicol  | T02-55/1407043-01 | 1              |
| Caelo                    | Chloramphenicol  | 310311            | 1              |
| Euro OTC                 | Chloramphenicol  | 314Q1259          | 1              |
| Caelo                    | Chloramphenicol  | 9323807           | 1              |
| Euro OTC                 | Chloramphenicol  | 1012013-01        | 2              |
| Caelo                    | Chloramphenicol  | 10341703          | 1              |
| Caelo                    | Chloramphenicol  | 10341707          | 1              |
| Phönix                   | Chloramphenicol  | 10341710          | 1              |
| Caelo                    | Chloramphenicol  | 10341711          | 2              |
| Phönix                   | Chloramphenicol  | 10341716          | 1              |
| Caelo                    | Chloramphenicol  | 10341717          | 1              |
| Caelo                    | Chloramphenicol  | 11031402          | 1              |
| Euro OTC                 | Chloramphenicol  | 1107002-01        | 2              |
| Caelo                    | Chloramphenicol  | 1107002-01        | 1              |
| Gehe                     | Chloramphenicol  | 1107002-02        | 2              |
| ANZAG am 23.05.2012      | Chloramphenicol  | 1107002-02        | 2              |
| Euro OTC                 | Chloramphenicol  | 110700202         | 1              |
| Euro OTC                 | Chloramphenicol  | 1107002-02        | 1              |
| Caelo                    | Chloramphenicol  | 1137004           | 1              |
| Noweda                   | Chloramphenicol  | 1137014           | 1              |
| Caelo                    | Chloramphenicol  | 1137070           | 1              |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|----------------------------|------------------|--------------|----------------|
| Caelo                      | Chloramphenicol  | 11370702     | 5              |
| Caelo                      | Chloramphenicol  | 11370703     | 6              |
| Caelo                      | Chloramphenicol  | 11370705     | 4              |
| Anzag 15.11.2012           | Chloramphenicol  | 11370705     | 1              |
| Caelo                      | Chloramphenicol  | 11370707     | 2              |
| Phönix Gotha               | Chloramphenicol  | 11370711     | 1              |
| Bombastus                  | Chloramphenicol  | 11370711     | 1              |
| Anzag ek:2.98EUR 25.08.12  | Chloramphenicol  | 11370711     | 1              |
| Caesar & Loretz GmbH       | Chloramphenicol  | 11370711     | 1              |
| Anzag, 24.10.2012          | Chloramphenicol  | 11370711     | 2              |
| Sanacorp                   | Chloramphenicol  | 11370711     | 1              |
| Klenk                      | Chloramphenicol  | 11370711     | 1              |
| Noweda                     | Chloramphenicol  | 11370712     | 1              |
| Caelo                      | Chloramphenicol  | 11370712     | 3              |
| Caelo                      | Chloramphenicol  | 11370713     | 3              |
| Caelo                      | Chloramphenicol  | 11370714     | 2              |
| Caelo                      | Chloramphenicol  | 11370715     | 1              |
| Caelo                      | Chloramphenicol  | 11370716     | 5              |
| Caelo                      | Chloramphenicol  | 11370717     | 2              |
| Caelo                      | Chloramphenicol  | 1137714      | 1              |
| Fagron                     | Chloramphenicol  | 11J14-N03    | 1              |
| Fagron                     | Chloramphenicol  | 1202500003   | 1              |
| Euro OTC                   | Chloramphenicol  | 1203012-01   | 8              |
| Kehr                       | Chloramphenicol  | 1203012-01   | 1              |
| Gehe                       | Chloramphenicol  | 1203012-01   | 1              |
| Euro OCT                   | Chloramphenicol  | 1203012-02   | 2              |
| Kehr                       | Chloramphenicol  | 1203012-02   | 1              |
| Euro OTC                   | Chloramphenicol  | 1203012-12   | 1              |
| Caelo                      | Chloramphenicol  | 12072606     | 1              |
| Euro OTC                   | Chloramphenicol  | 1209019-01   | 10             |
| Anzag 12.03.2013           | Chloramphenicol  | 1209019-01   | 2              |
| Gehe                       | Chloramphenicol  | 1209019-01   | 1              |
| Gehe                       | Chloramphenicol  | 1209019-02   | 1              |
| Euro OTC                   | Chloramphenicol  | 120901902    | 3              |
| Alliance Health            | Chloramphenicol  | 1209019-02   | 1              |
| Caelo                      | Chloramphenicol  | 12101302     | 1              |
| Caelo                      | Chloramphenicol  | 12248501     | 15             |
| Phönix Gotha               | Chloramphenicol  | 12248501     | 1              |
| Phönix 11.03.13            | Chloramphenicol  | 12248501     | 1              |
| vdl                        | Chloramphenicol  | 12248501     | 1              |
| Anzag 03.04.13 ek: 3,18EUR | Chloramphenicol  | 12248501     | 1              |
| GEHE                       | Chloramphenicol  | 12248501     | 1              |
| Sanacorp                   | Chloramphenicol  | 12248501     | 1              |
| Caelo                      | Chloramphenicol  | 12248505     | 4              |
| Caelo                      | Chloramphenicol  | 12248506     | 8              |
| Caelo                      | Chloramphenicol  | 12248507     | 9              |
| Sanacorp                   | Chloramphenicol  | 12248507     | 1              |
| AHD                        | Chloramphenicol  | 12248507     | 1              |
| Caelo                      | Chloramphenicol  | 12248509     | 13             |
| Noweda                     | Chloramphenicol  | 12248509     | 1              |
| EuRho/Phönix               | Chloramphenicol  | 123012-01    | 1              |
| Phönix 11.11.2014          | Chloramphenicol  | 12448509     | 1              |
| Fagron                     | Chloramphenicol  | 12A11-N02    | 1              |
| Noweda                     | Chloramphenicol  | 12B13-N06    | 1              |
| Fagron                     | Chloramphenicol  | 12F01-N23    | 1              |
| Fagron                     | Chloramphenicol  | 12G02-N01    | 11             |
| Caelo                      | Chloramphenicol  | 12G02-N01    | 2              |
| Noweda                     | Chloramphenicol  | 12G02-N01    | 1              |
| Caelo                      | Chloramphenicol  | 12g02n01     | 1              |
| Fagron                     | Chloramphenicol  | 12L11-N06    | 10             |

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| Supplier              | Substance       | Batch            | Spectra |
|-----------------------|-----------------|------------------|---------|
| Phönix                | Chloramphenicol | 1302024-01       | 1       |
| Caelo                 | Chloramphenicol | 1302024-01       | 1       |
| Caelo                 | Chloramphenicol | 1302024-02       | 2       |
| Euro OTC              | Chloramphenicol | 1302034-01       | 1       |
| Caelo                 | Chloramphenicol | 130416-1         | 1       |
| Caelo                 | Chloramphenicol | 130416-2         | 1       |
| Euro OTC              | Chloramphenicol |                  | 2       |
| Caelo                 | Chloramphenicol | 13080902         | 1       |
| Phoenix               | Chloramphenicol | 13080903         | 1       |
| Phönix                | Chloramphenicol | 13A11-N02        | 5       |
| Fagron                | Chloramphenicol | 13A11N02         | 1       |
| FARGON                | Chloramphenicol | 13a11-n02        | 1       |
| ADH, 11.10.2013       | Chloramphenicol | 13A11-N02        | 1       |
| Caelo                 | Chloramphenicol | 13A31-B02        | 1       |
| Fagron                | Chloramphenicol | 13A31-B02-286708 | 1       |
| Phönix                | Chloramphenicol | 1436907          | 1       |
| Euro OTC              | Chloramphenicol | 1509211259       | 1       |
| Caelo                 | Chloramphenicol | 20102012J1       | 1       |
| Euro OTC              | Chloramphenicol | 2121211203012-0  | 1       |
| Caelo                 | Chloramphenicol | 28011401         | 1       |
| Caelo                 | Chloramphenicol | 3125204          | 1       |
| Sanacorp              | Chloramphenicol | 41/AKD23         | 1       |
| Caelo                 | Chloramphenicol | 4712Q-01259      | 1       |
| Gatt-Koller / Phoenix | Chloramphenicol | 5615/12115211    | 1       |
| Caelo                 | Chloramphenicol | 70777297         | 1       |
| Northeast Gen         | Chloramphenicol | DY122127         | 1       |
| Caelo                 | Chloramphenicol | DY00911233       | 1       |
| Caelo                 | Chloramphenicol | 11/14-N03        | 2       |
| EUro/AHD              | Chloramphenicol | 1209019-01       | 1       |
| EUro/AHD              | Chloramphenicol | 1209019-02       | 1       |
| AHD                   | Chloramphenicol | 12248509         | 1       |
| Fragon                | Chloramphenicol | 12G02-N01        | 1       |
| Fagron                | Chloramphenicol | 1G02N01          | 1       |
| GEHE                  | Chloramphenicol | 21022141/2       | 1       |

- 68 851 spectra from 414 *Apo-Ident* customers from a total of 23 632 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Chloramphenicol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Chloramphenicol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 450           | 0              | 70 936        |
| Type B | 0              | 315           | 0              | 146 414       |
| Type C | 0              | 777           | 5              | 68 851        |

The substance/substance group *Chloramphenicol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.6667 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.0952 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 99.3606 % (> 98.9770 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 20777            | 20777                      | 0.00                                | 38.21                                  |
| 20787            | 22367                      | 11.17                               | 35.16                                  |
| 20807            | 22367                      | 7.35                                | 35.95                                  |
| 20813            | 20777                      | 1.99                                | 37.92                                  |
| 20822            | 20777                      | 2.20                                | 37.82                                  |
| 21701            | 21701                      | 0.00                                | 35.38                                  |
| 21752            | 22367                      | 7.93                                | 37.76                                  |
| 21910            | 22367                      | 4.02                                | 36.88                                  |
| 21988            | 21701                      | 5.56                                | 34.81                                  |
| 22367            | 22367                      | 0.00                                | 37.03                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Chlorhexidine diacetate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20989-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Chlorhexidine diacetate; Chlorhexidini acetat; Chlorhexidinum aceticum

### Special notes

When selecting the *Chlorhexidine diacetate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Chlorhexidine diacetate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Caelo    | Chlorhexidine di... | 12142726         | 20989     | 40      | 1402685     |
| Caelo    | Chlorhexidine di... | 12142727         | 21041     | 40      | 20120711    |
| Fagron   | Chlorhexidine di... | 14I08-B02-306223 | 22280     | 40      | 20140922    |
| Caelo    | Chlorhexidine di... | 154389           | 22456     | 40      | 20160309*   |
| Caelo    | Chlorhexidine di... | 15438914         | 22900     | 40      | 1704392     |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Chlorhexidine di... | 15J02-B08-322916 | 22947     | 40      | 20151104    |
| Caelo    | Chlorhexidine di... | 15438913         | 23041     | 40      | 20160309*   |
| Caelo    | Chlorhexidine di... | 154389           | 23042     | 40      | 2060309*    |
| Caelo    | Chlorhexidine di... | 154389           | 23043     | 40      | 2060309*    |
| Caelo    | Chlorhexidine di... | 15438909         | 23044     | 40      | 2060309*    |
| Caelo    | Chlorhexidine di... | 154389           | 23048     | 40      | 2060309*    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 440 spectra of 11 reference samples from the substance/substance group *Chlorhexidine diacetate*. These samples are listed above in the [calibration samples](#) section.
- 70 946 spectra from a total of 1544 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 7 reference samples from the substance/substance group *Chlorhexidine diacetate*.

| Supplier | Substance               | Batch            | Sample ID          | Spectra |
|----------|-------------------------|------------------|--------------------|---------|
| Caelo    | Chlorhexidine diacetate | 9113914          | 20141              | 40      |
| Fagron   | Chlorhexidine diacetate | 14I08-B02-306223 | 22280 <sup>†</sup> | 20      |
| Caelo    | Chlorhexidine diacetate | 154389           | 22456 <sup>†</sup> | 20      |
| Fagron   | Chlorhexidine diacetate | 15J02-B08-322916 | 22946              | 40      |
| Caelo    | Chlorhexidine diacetate | 15438914         | 22951              | 40      |
| Caelo    | Chlorhexidine diacetate | 152610           | 23045              | 40      |
| Caelo    | Chlorhexidine diacetate | 171858           | 23640              | 40      |

- 146 489 spectra from a total of 3187 batches from further 862 substances. These spectra were

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 273 spectra from 162 *Apo-Ident* customers from 73 batches from the substance/substance group *Chlorhexidine diacetate*.

| Supplier                | Substance               | Batch            | Spectra |
|-------------------------|-------------------------|------------------|---------|
| Caelo                   | Chlorhexidine diacetate | 1072015C         | 1       |
| Caelo                   | Chlorhexidine diacetate | 9113904          | 3       |
| keine Angabe            | Chlorhexidine diacetate | 11204402         | 2       |
| Caelo                   | Chlorhexidine diacetate | 11204406         | 2       |
| Caelo                   | Chlorhexidine diacetate | 12142725         | 9       |
| Caelo                   | Chlorhexidine diacetate | 12142726         | 8       |
| Caelo                   | Chlorhexidine diacetate | 12142727         | 9       |
| Noweda                  | Chlorhexidine diacetate | 12142727         | 1       |
| Großhandel              | Chlorhexidine diacetate | 12142734         | 1       |
| Caelo                   | Chlorhexidine diacetate | 12142734         | 10      |
| GEHE                    | Chlorhexidine diacetate | 12142734         | 1       |
| Phoenix                 | Chlorhexidine diacetate | 12142734         | 1       |
| Caelo                   | Chlorhexidine diacetate | 12177503         | 3       |
| Caelo                   | Chlorhexidine diacetate | 13177001         | 5       |
| Caelo                   | Chlorhexidine diacetate | 13177002         | 11      |
| Caelo                   | Chlorhexidine diacetate | 13177002         | 2       |
| Phoenix                 | Chlorhexidine diacetate | 13177002         | 1       |
| Caelo                   | Chlorhexidine diacetate | 13177007         | 14      |
| Medichem S.A. ES/Noweda | Chlorhexidine diacetate | 13177007         | 1       |
| Caelo                   | Chlorhexidine diacetate | 13177008         | 2       |
| Caelo                   | Chlorhexidine diacetate | 13177009         | 3       |
| Caelo                   | Chlorhexidine diacetate | 13177021         | 14      |
| Caelo                   | Chlorhexidine diacetate | 13177022         | 2       |
| Caelo                   | Chlorhexidine diacetate | 13177024         | 4       |
| Fagron                  | Chlorhexidine diacetate | 13E03-B06-287926 | 2       |
| Caelo                   | Chlorhexidine diacetate | 15261003         | 7       |
| Euro OTC                | Chlorhexidine diacetate | 15261004         | 1       |
| Caelo                   | Chlorhexidine diacetate | 15261004         | 1       |
| Caelo                   | Chlorhexidine diacetate | 15261005         | 3       |
| Caelo                   | Chlorhexidine diacetate | 15261007         | 9       |
| Caelo                   | Chlorhexidine diacetate | 15261009         | 8       |
| Caelo                   | Chlorhexidine diacetate | 15261012         | 2       |
| Caelo                   | Chlorhexidine diacetate | 15261014         | 12      |
| Caelo                   | Chlorhexidine diacetate | 15438902         | 4       |
| Wepa/Wepa               | Chlorhexidine diacetate | 15438902         | 1       |
| Caelo                   | Chlorhexidine diacetate | 15438903         | 6       |
| Caelo                   | Chlorhexidine diacetate | 15438909         | 1       |
| Caelo                   | Chlorhexidine diacetate | 15438911         | 4       |
| Caelo                   | Chlorhexidine diacetate | 15438914         | 1       |
| Caelo                   | Chlorhexidine diacetate | 15438917         | 4       |
| Phoenix                 | Chlorhexidine diacetate | 15438917         | 1       |
| Phönix                  | Chlorhexidine diacetate | 15438917         | 1       |
| Caelo                   | Chlorhexidine diacetate | 23012015D        | 1       |
| Caelo                   | Chlorhexidine diacetate | 31032014B        | 1       |
| Sanacorp                | Chlorhexidine diacetate | 7/AKD6           | 1       |
| Sanacorp                | Chlorhexidine diacetate |                  | 1       |

*continued on the next page*



continued from previous page

| Supplier                   | Substance               | Batch          | Spectra |
|----------------------------|-------------------------|----------------|---------|
| Caelo                      | Chlorhexidine diacetate | 9113903        | 1       |
| Phönix                     | Chlorhexidine diacetate | 9113916        | 2       |
| Caelo                      | Chlorhexidine diacetate | 10154407       | 1       |
| Caelo                      | Chlorhexidine diacetate | 10154412       | 1       |
| Caelo                      | Chlorhexidine diacetate | 10154421       | 1       |
| Caelo                      | Chlorhexidine diacetate | 10154424       | 1       |
| Caelo                      | Chlorhexidine diacetate | 10154429       | 1       |
| Euro OTC                   | Chlorhexidine diacetate | 10154430       | 1       |
| Caelo                      | Chlorhexidine diacetate | 1091139389     | 1       |
| ANZAG am 15.05.2012        | Chlorhexidine diacetate | 11204401       | 2       |
| Caelo                      | Chlorhexidine diacetate | 11204401       | 3       |
| Caelo                      | Chlorhexidine diacetate | 11204405       | 1       |
| Anzag 17.07.2012           | Chlorhexidine diacetate | 11204405       | 1       |
| Caelo                      | Chlorhexidine diacetate | 11204407       | 1       |
| Caelo                      | Chlorhexidine diacetate | 11204408       | 3       |
| Phoenix                    | Chlorhexidine diacetate | 11204408       | 1       |
| Fagron                     | Chlorhexidine diacetate | 11L28N02       | 1       |
| Caelo                      | Chlorhexidine diacetate | 12142702       | 3       |
| phoenix                    | Chlorhexidine diacetate | 12142704       | 1       |
| Caelo                      | Chlorhexidine diacetate | 12142704       | 4       |
| Caesar&loretz,Anzag        | Chlorhexidine diacetate | 12142704       | 1       |
| Caelo                      | Chlorhexidine diacetate | 12142704ok     | 1       |
| Caelo                      | Chlorhexidine diacetate | 12142705       | 3       |
| Caelo                      | Chlorhexidine diacetate | 12142709       | 1       |
| Caelo                      | Chlorhexidine diacetate | 12142715       | 3       |
| Caelo                      | Chlorhexidine diacetate | 12142720       | 11      |
| Noweda                     | Chlorhexidine diacetate | 12142720       | 1       |
| Caesar & Loretz GmbH, 4... | Chlorhexidine diacetate | 12142720       | 1       |
| Sanacorp                   | Chlorhexidine diacetate | 12142726       | 1       |
| Phoenix                    | Chlorhexidine diacetate | 12142726       | 1       |
| Sanacorp                   | Chlorhexidine diacetate | 12142734       | 1       |
| Caelo                      | Chlorhexidine diacetate | 12177502       | 1       |
| Caelo                      | Chlorhexidine diacetate | 12177504       | 1       |
| Caelo                      | Chlorhexidine diacetate | 12177505       | 6       |
| Großhandel                 | Chlorhexidine diacetate | 12177505       | 1       |
| Caelo                      | Chlorhexidine diacetate | 12177510       | 10      |
| Alliance Healthcare        | Chlorhexidine diacetate | 12177510       | 1       |
| Caelo                      | Chlorhexidine diacetate | 123456         | 1       |
| Caelo                      | Chlorhexidine diacetate | 1242720        | 1       |
| Caelo                      | Chlorhexidine diacetate | 1602211263     | 1       |
| Fagron                     | Chlorhexidine diacetate | 1-8991-1-01-01 | 1       |
| phönix                     | Chlorhexidine diacetate |                | 1       |
| Anzag                      | Chlorhexidine diacetate | 70558377       | 1       |
| Ceasar & Loretz GmbH       | Chlorhexidine diacetate | 80104278       | 1       |
| Caelo                      | Chlorhexidine diacetate | 91139389       | 1       |
| Fagron                     | Chlorhexidine diacetate | A-130037       | 1       |
| Phönix                     | Chlorhexidine diacetate | Retest09113916 | 1       |
| Anzag                      | Chlorhexidine diacetate | 12177505       | 1       |
| Fiebig                     | Chlorhexidine diacetate | 12C19-N02      | 1       |
| Fagron                     | Chlorhexidine diacetate | 12E14-N11      | 1       |
| Sanacorp                   | Chlorhexidine diacetate | 12142709       | 1       |
| Caelo                      | Chlorhexidine diacetate | 1214726        | 1       |

- 69 360 spectra from 414 *Apo-Ident* customers from a total of 23 730 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),



the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Chlorhexidine diacetate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Chlorhexidine diacetate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 440           | 0              | 70 946        |
| <b>Type B</b> | 0              | 240           | 0              | 146 489       |
| <b>Type C</b> | 0              | 267           | 6              | 69 360        |

The substance/substance group *Chlorhexidine diacetate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.6364 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 97.8022 % (> 96.7033 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20989     | 20989               | 0.00                         | 26.89                           |
| 21041     | 20989               | 7.99                         | 27.01                           |
| 22280     | 20989               | 7.49                         | 26.96                           |
| 22456     | 22456               | 0.00                         | 27.78                           |
| 22900     | 22900               | 0.00                         | 28.42                           |
| 22947     | 20989               | 4.78                         | 26.89                           |
| 23041     | 23041               | 0.00                         | 26.99                           |
| 23042     | 23042               | 0.00                         | 27.03                           |
| 23043     | 23043               | 0.00                         | 27.13                           |
| 23044     | 23044               | 0.00                         | 27.11                           |
| 23048     | 23048               | 0.00                         | 27.20                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Chlorhexidine dihydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20198-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Chlorhexidine dihydrochloride; Chlorhexidini dihydrochloridum; Chlorhexidinum dihydrochloricum

### Special notes

When selecting the *Chlorhexidine dihydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Chlorhexidine dihydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Chlorhexidine di... | 14A09-B03-290724 | 21225     | 40      | AR-15-FG-012308-01 |
| Fagron   | Chlorhexidine di... | 16C11-B02-322510 | 23209     | 40      | 20160412           |
| Fagron   | Chlorhexidine di... | 16C11-B02-329881 | 23230     | 40      | 20160412           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Chlorhexidine dihydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *Chlorhexidine dihydrochloride*.

| Supplier | Substance                     | Batch            | Sample ID | Spectra |
|----------|-------------------------------|------------------|-----------|---------|
| Fagron   | Chlorhexidine dihydrochloride | 10B02-N06        | 20198     | 40      |
| Fagron   | Chlorhexidine dihydrochloride | 16C11-B02-324203 | 22805     | 40      |

- 146 649 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 2 spectra from 2 *Apo-Ident* customers from 2 batches from the substance/substance group *Chlorhexidine dihydrochloride*.

| Supplier | Substance                     | Batch            | Spectra |
|----------|-------------------------------|------------------|---------|
| Fagron   | Chlorhexidine dihydrochloride | 14A09B03         | 1       |
| Fagron   | Chlorhexidine dihydrochloride | 14A09-B03-293425 | 1       |

- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Chlorhexidine dihydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Chlorhexidine dihydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 40            | 40             | 146 649       |
| <b>Type C</b> | 0              | 1             | 1              | 69 631        |

The substance/substance group *Chlorhexidine dihydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 50.0000 % (> 46.2500 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21225     | 21225               | 0.00                         | 33.15                           |
| 23209     | 21225               | 3.29                         | 32.89                           |
| 23230     | 21225               | 3.80                         | 32.81                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Chlorocresol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20185-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Chlorocresol; Chlorocresolum

### Special notes

When selecting the *Chlorocresol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Chlorocresol*:

| Supplier | Substance    | Batch    | Sample ID | Spectra | Certificate |
|----------|--------------|----------|-----------|---------|-------------|
| Caelo    | Chlorocresol | 13275106 | 21512     | 40      | 20130828    |
| Caelo    | Chlorocresol | 13275106 | 21513     | 40      | 20130828    |
| Caelo    | Chlorocresol | 163378   | 23357     | 40      | 20170124*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Chlorocresol*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 170 spectra of 5 reference samples from the substance/substance group *Chlorocresol*.

| Supplier | Substance    | Batch    | Sample ID          | Spectra |
|----------|--------------|----------|--------------------|---------|
| Caelo    | Chlorocresol | 9282613  | 20185              | 50      |
| Caelo    | Chlorocresol | 1211107  | 21306              | 40      |
| Caelo    | Chlorocresol | 13275106 | 21512 <sup>†</sup> | 20      |
| Caelo    | Chlorocresol | 13275106 | 21513 <sup>†</sup> | 20      |
| Caelo    | Chlorocresol | 15114107 | 23411              | 40      |

- 146 559 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 17 spectra from 14 *Apo-Ident* customers from 10 batches from the substance/substance group *Chlorocresol*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier | Substance    | Batch       | Spectra |
|----------|--------------|-------------|---------|
| Caelo    | Chlorocresol | 12111013    | 3       |
| Caelo    | Chlorocresol | 2041513     | 1       |
| Caelo    | Chlorocresol | 12111017    | 2       |
| Caelo    | Chlorocresol | 13275117    | 1       |
| Caelo    | Chlorocresol | 15114103    | 1       |
| Caelo    | Chlorocresol | 4613M-01260 | 1       |
| Caelo    | Chlorocresol | 7061304     | 1       |
| Caelo    | Chlorocresol | 10145239    | 4       |
| Caelo    | Chlorocresol | 23415422    | 1       |
| Noweda   | Chlorocresol | 12111017    | 1       |
| GEHE     | Chlorocresol | 10145219    | 1       |

- 69 616 spectra from 414 *Apo-Ident* customers from a total of 23 791 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Chlorocresol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Chlorocresol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 161           | 9              | 146 559       |
| <b>Type C</b> | 0              | 16            | 1              | 69 616        |

The substance/substance group *Chlorocresol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 94.7059 % (> 92.9412 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21512     | 23357               | 15.63                        | 37.96                           |
| 21513     | 23357               | 15.38                        | 35.13                           |
| 23357     | 23357               | 0.00                         | 27.72                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Chlortetracycline hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20845-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Chlortetracycline hydrochloride; Chlortetracyclini hydrochloridum; Chlortetracyclinum hydrochloricum

### Special notes

When selecting the *Chlortetracycline hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Chlortetracycline hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Chlortetracyclin... | 12K30-N07        | 20845     | 40      | 1405318     |
| Fagron   | Chlortetracyclin... | 12K30-N07        | 21222     | 40      | 20121210    |
| Euro OTC | Chlortetracyclin... | 1108051-02       | 21241     | 40      | 20111013    |
| Fagron   | Chlortetracyclin... | 14J08-B07-307742 | 21877     | 40      | 20141029    |
| Euro OTC | Chlortetracyclin... | 1604015          | 22541     | 40      | 20160510*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Chlortetracycline - hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 130 spectra of 4 reference samples from the substance/substance group *Chlortetracycline - hydrochloride*.

| Supplier | Substance                       | Batch            | Sample ID          | Spectra |
|----------|---------------------------------|------------------|--------------------|---------|
| Fagron   | Chlortetracycline hydrochlor... | 7C27-N01         | 20119              | 40      |
| Fagron   | Chlortetracycline hydrochlor... | 14J08-B07-307742 | 21877 <sup>†</sup> | 20      |
| Euro OTC | Chlortetracycline hydrochlor... | 1604015-01       | 22975              | 40      |
| Fagron   | Chlortetracycline hydrochlor... | 16B10-B09-329778 | 23571              | 30      |

- 146 599 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 129 spectra from 76 *Apo-Ident* customers from 42 batches from the substance/substance group *Chlortetracycline hydrochloride*.

| Supplier                | Substance                       | Batch            | Spectra |
|-------------------------|---------------------------------|------------------|---------|
| Fagron                  | Chlortetracycline hydrochlor... | 12K30-N07        | 10      |
| Euro OTC                | Chlortetracycline hydrochlor... | 1412008-02       | 11      |
| Nachprüfung 2574        | Chlortetracycline hydrochlor... | 1108051-01       | 1       |
| Nachprüfung             | Chlortetracycline hydrochlor... | 1108051-01       | 3       |
| Phoenix                 | Chlortetracycline hydrochlor... | 110805102        | 1       |
| Euro                    | Chlortetracycline hydrochlor... | 1108051-02       | 1       |
| Phönix                  | Chlortetracycline hydrochlor... | 1108051-02       | 2       |
| Fagron                  | Chlortetracycline hydrochlor... | 13/11-N07        | 4       |
| Fagron                  | Chlortetracycline hydrochlor... | 13K26-N06        | 3       |
| Euro OTC                | Chlortetracycline hydrochlor... | 1412008-01       | 3       |
| Caelo                   | Chlortetracycline hydrochlor... | 1412008-01       | 1       |
| Euro OTC                | Chlortetracycline hydrochlor... | 141200802        | 2       |
| Caelo                   | Chlortetracycline hydrochlor... | 1412008-02       | 1       |
| Euro OTC                | Chlortetracycline hydrochlor... | 1412008-03       | 3       |
| Caelo                   | Chlortetracycline hydrochlor... | 141200803        | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 14J08-B07        | 4       |
| Caelo                   | Chlortetracycline hydrochlor... | 14J08-B07-300249 | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 14J08B07300250   | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 14J08-B07-300250 | 7       |
| Fagron                  | Chlortetracycline hydrochlor... | 14J08-B07-303352 | 3       |
| Caelo                   | Chlortetracycline hydrochlor... | 14J08-B07-303352 | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 14J08-B07-307100 | 5       |
| Euro OTC                | Chlortetracycline hydrochlor... | 1604015-01       | 2       |
| EuRo/Phönix             | Chlortetracycline hydrochlor... | 160401501        | 1       |
| Gehe                    | Chlortetracycline hydrochlor... | 16B10-B09        | 1       |
| Caelo                   | Chlortetracycline hydrochlor... | 16B10-B09-318088 | 3       |
| Fagron                  | Chlortetracycline hydrochlor... | 16B10-B09-318088 | 2       |
| Gehe                    | Chlortetracycline hydrochlor... | 16B10-B09-322715 | 1       |
| Gehe                    | Chlortetracycline hydrochlor... | 16B10-B09-322716 | 1       |
| Phoenix                 | Chlortetracycline hydrochlor... | 16B10-B09-322716 | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 4/AKD6           | 1       |
| Euro OTC                | Chlortetracycline hydrochlor... | 4612Q-01155      | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | FC11051038       | 1       |
| Caelo                   | Chlortetracycline hydrochlor... | FC13030134       | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | FC15100204       | 1       |
| Euro OTC                | Chlortetracycline hydrochlor... | 1108051-01       | 9       |
| Sanacorp                | Chlortetracycline hydrochlor... | 1108051-01       | 1       |
| Euro OTC                | Chlortetracycline hydrochlor... | 1108051-02       | 6       |
| Euro OTC                | Chlortetracycline hydrochlor... | 110805102        | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 12C16-N01        | 3       |
| Noweda                  | Chlortetracycline hydrochlor... | 12c16-n01        | 1       |
| Caesar & Loretz GmbH    | Chlortetracycline hydrochlor... | 12C16-N01        | 1       |
| Anzag; 07.09.12 ek:4.01 | Chlortetracycline hydrochlor... | 12C16-N01        | 1       |
| Krieger                 | Chlortetracycline hydrochlor... | 12C16-No1        | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 12H28-N09        | 7       |
| Fagron                  | Chlortetracycline hydrochlor... | 12H28N09         | 1       |
| Alliance Healthcare     | Chlortetracycline hydrochlor... | 12K30-N07        | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 12k30-N07        | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 12K30-N07        | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 13111-N07        | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 27121306         | 1       |
| Euro OTC                | Chlortetracycline hydrochlor... | 2901009V-03      | 1       |
| Euro OTC                | Chlortetracycline hydrochlor... | 5113I01155       | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | FC13030134       | 1       |
| Noweda                  | Chlortetracycline hydrochlor... | 11K25-N13        | 1       |
| EUro/AHD                | Chlortetracycline hydrochlor... | 1108051-02       | 1       |
| Fagron                  | Chlortetracycline hydrochlor... | 12h28-n09        | 1       |

- 69 504 spectra from 414 *Apo-Ident* customers from a total of 23 759 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Chlortetracycline hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Chlortetracycline hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 130           | 0              | 146 599       |
| <b>Type C</b> | 0              | 122           | 7              | 69 504        |

The substance/substance group *Chlortetracycline hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.3846 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 94.5736 % (> 92.2481 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20845     | 20845               | 0.00                         | 31.17                           |
| 21222     | 20845               | 6.59                         | 33.28                           |
| 21241     | 20845               | 6.95                         | 31.83                           |
| 21877     | 22541               | 6.61                         | 30.40                           |
| 22541     | 22541               | 0.00                         | 26.71                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Cholecalciferol dry concentrate</b>                          |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20921-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Cholecalciferol dry concentrate; Cholecalciferoli pulvis; Cholecalciferolum pulveratum

### Special notes

When selecting the *Cholecalciferol dry concentrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cholecalciferol dry concentrate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Euro OTC | Cholecalciferol ... | 1210051-01 | 20921     | 40      | 1403341     |
| Euro OTC | Cholecalciferol ... | 1502021-01 | 21914     | 40      | 20150309    |
| Euro OTC | Cholecalciferol ... | 1508032    | 21949     | 40      | 20150901*   |
| Euro OTC | Cholecalciferol ... | 1701053    | 23007     | 40      | 20170208*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Cholecalciferol dry concentrate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 6 reference samples from the substance/substance group *Cholecalciferol dry concentrate*.

| Supplier | Substance                       | Batch      | Sample ID          | Spectra |
|----------|---------------------------------|------------|--------------------|---------|
| Euro OTC | Cholecalciferol dry concentr... | 1103005-01 | 20353              | 40      |
| Euro OTC | Cholecalciferol dry concentr... | 1304016-02 | 21240              | 40      |
| Euro OTC | Cholecalciferol dry concentr... | 1502021-01 | 21914 <sup>†</sup> | 20      |
| Euro OTC | Cholecalciferol dry concentr... | 1508032    | 21949 <sup>†</sup> | 20      |
| Euro OTC | Cholecalciferol dry concentr... | 1602019    | 22504              | 40      |
| Euro OTC | Cholecalciferol dry concentr... | 1608002    | 22749              | 40      |

- 146 529 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 8 spectra from 6 *Apo-Ident* customers from 7 batches from the substance/substance group *Cholecalciferol dry concentrate*.

| Supplier | Substance                       | Batch       | Spectra |
|----------|---------------------------------|-------------|---------|
| Euro OTC | Cholecalciferol dry concentr... | 1012025-01  | 1       |
| Euro OTC | Cholecalciferol dry concentr... | 1502021-01  | 1       |
| Caelo    | Cholecalciferol dry concentr... | 1602019-01  | 1       |
| Euro OTC | Cholecalciferol dry concentr... | 1210051-01  | 2       |
| Euro OTC | Cholecalciferol dry concentr... | L1403012-01 | 1       |
| Euro OTC | Cholecalciferol dry concentr... | 1304016-01  | 1       |
| Euro OTC | Cholecalciferol dry concentr... | P500238     | 1       |

- 69 625 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cholecalciferol dry concentrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cholecalciferol dry concentrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 171           | 29             | 146 524       |
| <b>Type C</b> | 0              | 7             | 1              | 69 625        |

The substance/substance group *Cholecalciferol dry concentrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 85.5000 % (> 84.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested

reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20921     | 20921               | 0.00                         | 39.34                           |
| 21914     | 21949               | 1.76                         | 29.05                           |
| 21949     | 21949               | 0.00                         | 28.68                           |
| 23007     | 23007               | 0.00                         | 39.60                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Cholesterol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20446-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Cholesterol; Cholesterinum; Cholesterolum

### Special notes

When selecting the *Cholesterol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cholesterol*:

| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate |
|----------|-------------|------------------|-----------|---------|-------------|
| Fagron   | Cholesterol | 13F10-B40        | 21219     | 40      | 20131223    |
| Caelo    | Cholesterol | 160444           | 22461     | 40      | 20160222*   |
| Fagron   | Cholesterol | 15J23-B03-325106 | 22971     | 20      | 20151103    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 100 spectra of 3 reference samples from the substance/substance group *Cholesterol*. These samples are listed above in the [calibration samples](#) section.
- 71 286 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 7 reference samples from the substance/substance group *Cholesterol*.

| Supplier | Substance   | Batch            | Sample ID          | Spectra |
|----------|-------------|------------------|--------------------|---------|
| Fagron   | Cholesterol | 10315-N07        | 20446              | 40      |
| Caelo    | Cholesterol | 11242104         | 20459              | 40      |
| Fagron   | Cholesterol | 8L09-N01         | 20510              | 40      |
| Caelo    | Cholesterol | 13148703         | 21310              | 40      |
| Caelo    | Cholesterol | 160444           | 22461 <sup>†</sup> | 20      |
| Fagron   | Cholesterol | 15J23-B03-325106 | 22971 <sup>†</sup> | 20      |
| Fagron   | Cholesterol | 16G05-B03-331396 | 23522              | 40      |

- 146 489 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 55 spectra from 32 *Apo-Ident* customers from 38 batches from the substance/substance group *Cholesterol*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier           | Substance   | Batch            | Spectra |
|--------------------|-------------|------------------|---------|
| Caelo              | Cholesterol | 12248403         | 1       |
| Fagron             | Cholesterol | 12I13-N02        | 2       |
| Fagron             | Cholesterol | 13C25-N12        | 2       |
| Fagron             | Cholesterol | 13F10-B40        | 1       |
| Fagron             | Cholesterol | 13F10-B40-289016 | 2       |
| Fagron             | Cholesterol | 14B27-B05        | 1       |
| Fagron             | Cholesterol | 14B27-B05-293548 | 2       |
| Fagron             | Cholesterol | 14G04-B02-300830 | 1       |
| Caelo              | Cholesterol | 15358801         | 5       |
| Caelo              | Cholesterol | 15407101         | 2       |
| Fagron             | Cholesterol | 15B09-B02-308259 | 2       |
| Caelo              | Cholesterol | 15B09-B02-308259 | 1       |
| Fagron             | Cholesterol | 15G31-B05-312377 | 1       |
| Fagron             | Cholesterol | 15G31-B05-312378 | 1       |
| Caelo              | Cholesterol | 15J23-B03        | 1       |
| Fagron             | Cholesterol | 15J23-B03-320483 | 2       |
| Fagron             | Cholesterol | 15J23-B03-325106 | 1       |
| Fagron             | Cholesterol | 8J28-N10         | 1       |
| Fagron             | Cholesterol | 10H24-N06        | 1       |
| Caelo              | Cholesterol | 11242103         | 1       |
| Fagron             | Cholesterol | 11A17-N07        | 1       |
| Fagron             | Cholesterol | 13G10-N11        | 3       |
| Fagron             | Cholesterol | 2013U-01270      | 1       |
| Caelo              | Cholesterol | 13148704         | 1       |
| Caelo              | Cholesterol | 14122501         | 2       |
| Caelo              | Cholesterol | 14208602         | 1       |
| Fagron             | Cholesterol | 14G04-B02        | 1       |
| Caelo              | Cholesterol | 15028303         | 1       |
| Fagron             | Cholesterol | 15B09-B02        | 1       |
| Caelo              | Cholesterol | 15G31-B05-312376 | 1       |
| Fagron             | Cholesterol | 15G31-B05        | 2       |
| Fagron             | Cholesterol | 15G31-B05-316721 | 1       |
| Fagron             | Cholesterol |                  | 1       |
| Ebert-Jacobi       | Cholesterol | 16044408         | 1       |
| Caelo              | Cholesterol | 12155605         | 1       |
| Phönix, 23.05.2013 | Cholesterol | 12155605         | 1       |
| Fagron             | Cholesterol | 12D02-N10        | 1       |
| Caelo              | Cholesterol | 13056903         | 1       |
| Caelo              | Cholesterol | 14027201         | 1       |
| Fagron             | Cholesterol | 10B15-N07        | 1       |

- 69 578 spectra from 414 *Apo-Ident* customers from a total of 23 763 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cholesterol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cholesterol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 100           | 0              | 71 286        |
| Type B | 0              | 184           | 56             | 146 489       |
| Type C | 0              | 44            | 11             | 69 578        |

The substance/substance group *Cholesterol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 76.6667 % (> 75.4167 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 80.0000 % (> 74.5455 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21219     | 22461               | 14.04                        | 48.22                           |
| 22461     | 22461               | 0.00                         | 52.89                           |
| 22971     | 22461               | 17.83                        | 49.87                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Choline chloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22639-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Choline chloride; Cholinii chloridum

### Special notes

When selecting the *Choline chloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Choline chloride*:

| Supplier | Substance        | Batch    | Sample ID | Spectra | Certificate |
|----------|------------------|----------|-----------|---------|-------------|
| Caelo    | Choline chloride | 162092   | 22639     | 40      | 20160801*   |
| Caelo    | Choline chloride | 14273819 | 22663     | 40      | 20141002    |
| Caelo    | Choline chloride | 16209209 | 23582     | 40      | 20160801    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Choline chloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 70 spectra of 2 reference samples from the substance/substance group *Choline chloride*.

| Supplier | Substance        | Batch    | Sample ID | Spectra |
|----------|------------------|----------|-----------|---------|
| Caelo    | Choline chloride | 14273819 | 22734     | 40      |
| Caelo    | Choline chloride | 172053   | 23618     | 30      |

- 146 659 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Choline chloride*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Choline chloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Choline chloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 70            | 0              | 146 659       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Choline chloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 91.4286 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22639     | 22639               | 0.00                         | 106.17                          |
| 22663     | 22639               | 12.33                        | 106.12                          |
| 23582     | 22639               | 8.55                         | 106.42                          |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Choline hydrogen tartrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20719-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Choline hydrogen tartrate; Cholinii hyrogenotartras; Cholinium bitartaricum

### Special notes

When selecting the *Choline hydrogen tartrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Choline hydrogen tartrate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Euro OTC | Choline hydrogen... | 1603044    | 22549     | 40      | 20160429*   |
| Euro OTC | Choline hydrogen... | 1607020    | 22689     | 40      | 20160808*   |
| Euro OTC | Choline hydrogen... | 1603044-01 | 23010     | 40      | 20160429    |
| Euro OTC | Choline hydrogen... | 1702005    | 23130     | 40      | 20170307*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Choline hydrogen tartrate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 5 reference samples from the substance/substance group *Choline hydrogen tartrate*.

| Supplier | Substance                 | Batch          | Sample ID | Spectra |
|----------|---------------------------|----------------|-----------|---------|
| Dr. Behr | Choline hydrogen tartrate | WE-11030077-01 | 20427     | 40      |
| Euro OTC | Choline hydrogen tartrate | L1208016-01    | 20719     | 40      |
| Euro OTC | Choline hydrogen tartrate | L1208016-02    | 21242     | 40      |
| Euro OTC | Choline hydrogen tartrate | 1603044-01     | 23101     | 40      |
| Euro OTC | Choline hydrogen tartrate | 1707023        | 23610     | 40      |

- 146 529 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 13 spectra from 3 *Apo-Ident* customers from 7 batches from the substance/substance group *Choline hydrogen tartrate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier | Substance                 | Batch       | Spectra |
|----------|---------------------------|-------------|---------|
| Euro OTC | Choline hydrogen tartrate | 1303021-01  | 2       |
| Euro OTC | Choline hydrogen tartrate | 1309023-01  | 3       |
| Euro OTC | Choline hydrogen tartrate | 1405017-01  | 1       |
| Euro OTC | Choline hydrogen tartrate | 1501024-01  | 3       |
| Euro OTC | Choline hydrogen tartrate | 1603044-01  | 1       |
| Euro OTC | Choline hydrogen tartrate | 1607020-01  | 2       |
| Euro OTC | Choline hydrogen tartrate | L1208016-01 | 1       |

- 69 620 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Choline hydrogen tartrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Choline hydrogen tartrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 159           | 41             | 146 529       |
| <b>Type C</b> | 0              | 13            | 0              | 69 620        |

The substance/substance group *Choline hydrogen tartrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 79.5000 % (> 78.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22549     | 22549               | 0.00                         | 57.82                           |
| 22689     | 22689               | 0.00                         | 57.62                           |
| 23010     | 22549               | 2.59                         | 57.81                           |
| 23130     | 23130               | 0.00                         | 55.84                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ciclopirox olamine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20601-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ciclopirox olamine; Aminoethanolum Cicloproxi; Ciclopirox olaminum

### Special notes

When selecting the *Ciclopirox olamine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ciclopirox olamine*:

| Supplier | Substance          | Batch            | Sample ID | Spectra | Certificate        |
|----------|--------------------|------------------|-----------|---------|--------------------|
| Fagron   | Ciclopirox olamine | 13A16-N04        | 21218     | 40      | 20130117           |
| Caelo    | Ciclopirox olamine | 13343209         | 21298     | 40      | AR-15-FG-016214-01 |
| Caelo    | Ciclopirox olamine | 14147406         | 21655     | 40      | AR-15-FG-014857-01 |
| Fagron   | Ciclopirox olamine | 14F13-B03-302340 | 21964     | 40      | 1608170            |
| Caelo    | Ciclopirox olamine | 14378809         | 21991     | 40      | 20150227           |

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| Supplier | Substance          | Batch            | Sample ID | Spectra | Certificate        |
|----------|--------------------|------------------|-----------|---------|--------------------|
| Caelo    | Ciclopirox olamine | 15364408         | 23011     | 40      | 20151201           |
| Fagron   | Ciclopirox olamine | 16G26-B02-324884 | 23108     | 40      | 20160907           |
| Caelo    | Ciclopirox olamine | 14147406         | 21655SI   | 40      | AR-15-FG-014857-01 |
| Fagron   | Ciclopirox olamine | 14F13-B03-302340 | 21964SI   | 40      | 1608170            |
| Caelo    | Ciclopirox olamine | 14378809         | 21991SI   | 40      | 20150227           |
| Caelo    | Ciclopirox olamine | 15364408         | 23011SI   | 40      | 20151201           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 440 spectra of 11 reference samples from the substance/substance group *Ciclopirox olamine*. These samples are listed above in the [calibration samples](#) section.
- 70 946 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 520 spectra of 15 reference samples from the substance/substance group *Ciclopirox olamine*.

| Supplier | Substance          | Batch            | Sample ID            | Spectra |
|----------|--------------------|------------------|----------------------|---------|
| Caelo    | Ciclopirox olamine | pending          | 20558                | 40      |
| Fagron   | Ciclopirox olamine | 12B22-N03        | 20585                | 40      |
| Caelo    | Ciclopirox olamine | 12040904         | 20601                | 40      |
| Caelo    | Ciclopirox olamine | 12040906         | 20648                | 40      |
| Fagron   | Ciclopirox olamine | 14E21-M04        | 21594                | 60      |
| Caelo    | Ciclopirox olamine | 14147406         | 21655 <sup>†</sup>   | 20      |
| Fagron   | Ciclopirox olamine | 14F13-B03-302340 | 21964 <sup>†</sup>   | 20      |
| Caelo    | Ciclopirox olamine | 14378809         | 21991 <sup>†</sup>   | 20      |
| Fagron   | Ciclopirox olamine | 16G26-B02-324884 | 22969                | 40      |
| Fagron   | Ciclopirox olamine | 14E21-M04        | 21594SI              | 60      |
| Caelo    | Ciclopirox olamine | 14147406         | 21655SI <sup>†</sup> | 20      |
| Fagron   | Ciclopirox olamine | 14F13-B03-302340 | 21964SI <sup>†</sup> | 20      |
| Caelo    | Ciclopirox olamine | 14378809         | 21991SI <sup>†</sup> | 20      |
| Fagron   | Ciclopirox olamine | 16G26-B02-324884 | 22969SI              | 40      |
| Fagron   | Ciclopirox olamine | 16G26-B02-324884 | 23108SI              | 40      |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*).

- 146 209 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 80 spectra from 33 *Apo-Ident* customers from 44 batches from the substance/substance group *Ciclopirox olamine*.

| Supplier | Substance          | Batch            | Spectra |
|----------|--------------------|------------------|---------|
| Caelo    | Ciclopirox olamine | 13343201         | 2       |
| Caelo    | Ciclopirox olamine | 13343205         | 2       |
| Caelo    | Ciclopirox olamine | 13343207         | 1       |
| Caelo    | Ciclopirox olamine | 13343208         | 5       |
| Caelo    | Ciclopirox olamine | 13343209         | 3       |
| Caelo    | Ciclopirox olamine | 14147402         | 5       |
| Caelo    | Ciclopirox olamine | 14147403         | 2       |
| Caelo    | Ciclopirox olamine | 14147405         | 2       |
| Caelo    | Ciclopirox olamine | 14275801         | 2       |
| Caelo    | Ciclopirox olamine | 14275802         | 2       |
| Caelo    | Ciclopirox olamine | 14378801         | 3       |
| Caelo    | Ciclopirox olamine | 14378802         | 1       |
| Caelo    | Ciclopirox olamine | 14378803         | 1       |
| Caelo    | Ciclopirox olamine | 14378804         | 2       |
| Caelo    | Ciclopirox olamine | 14378805         | 2       |
| Caelo    | Ciclopirox olamine | 14378806         | 2       |
| Caelo    | Ciclopirox olamine | 14378810         | 2       |
| Caelo    | Ciclopirox olamine | 14378809         | 1       |
| Gehe     | Ciclopirox olamine | 14E21-M04        | 1       |
| Fagron   | Ciclopirox olamine | 14E21-M05        | 1       |
| Fagron   | Ciclopirox olamine | 14F13-B03-302339 | 1       |
| Caelo    | Ciclopirox olamine | 15018802         | 2       |
| Caelo    | Ciclopirox olamine | 15018803         | 1       |
| Caelo    | Ciclopirox olamine | 15364401         | 1       |
| Caelo    | Ciclopirox olamine | 15364402         | 1       |
| Caelo    | Ciclopirox olamine | 15364405         | 1       |
| Caelo    | Ciclopirox olamine | 15364407         | 2       |
| Caelo    | Ciclopirox olamine | 15364408         | 1       |
| Phoenix  | Ciclopirox olamine | 15364412         | 1       |
| Caelo    | Ciclopirox olamine | 17118802         | 1       |
| Sanacorp | Ciclopirox olamine | 17118806         | 1       |
| Euro OTC | Ciclopirox olamine | 17118806         | 1       |
| Caelo    | Ciclopirox olamine | 17118806         | 1       |
| Fagron   | Ciclopirox olamine | 10L09-N03        | 1       |
| Fagron   | Ciclopirox olamine | 11H03-N02        | 1       |
| Fagron   | Ciclopirox olamine | 11h03-n02        | 1       |
| Caelo    | Ciclopirox olamine | 12040903         | 1       |
| Caelo    | Ciclopirox olamine | 12040906         | 1       |
| Noweda   | Ciclopirox olamine | 12040911         | 1       |
| Caelo    | Ciclopirox olamine | 12040911         | 2       |

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Hence, these spectra are not independent and are not of *Type B*.

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| Supplier | Substance          | Batch     | Spectra |
|----------|--------------------|-----------|---------|
| Cael     | Ciclopirox olamine | 12040911  | 2       |
| Noweda   | Ciclopirox olamine | 12B22-N03 | 1       |
| Caelo    | Ciclopirox olamine | 12B22-N03 | 1       |
| Noweda   | Ciclopirox olamine | 12D26-N10 | 2       |
| Fagron   | Ciclopirox olamine | 12G12-N09 | 3       |
| Kehr     | Ciclopirox olamine | 12G12-N09 | 1       |
| Caelo    | Ciclopirox olamine | 13343     | 1       |
| Caelo    | Ciclopirox olamine | 13343202  | 1       |
| Fagron   | Ciclopirox olamine | 13A16-N04 | 1       |
| Fagron   | Ciclopirox olamine | G711016   | 1       |
| Phönix   | Ciclopirox olamine | 13A16-N04 | 1       |

- 69 553 spectra from 414 *Apo-Ident* customers from a total of 23 757 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ciclopirox olamine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ciclopirox olamine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 440           | 0              | 70 946        |
| <b>Type B</b> | 0              | 435           | 85             | 146 209       |
| <b>Type C</b> | 0              | 71            | 9              | 69 553        |

The substance/substance group *Ciclopirox olamine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.6364 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 83.6538 % (> 83.0769 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 88.7500 % (> 85.0000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested

reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21218     | 21964               | 8.48                         | 66.24                           |
| 21298     | 21298               | 0.00                         | 65.10                           |
| 21655     | 21655               | 0.00                         | 64.04                           |
| 21964     | 21964               | 0.00                         | 62.85                           |
| 21991     | 21298               | 4.58                         | 63.69                           |
| 23011     | 21298               | 6.51                         | 68.52                           |
| 23108     | 21964               | 5.19                         | 65.46                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ciclosporin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20941-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ciclosporin; Ciclosporinum

### Special notes

When selecting the *Ciclosporin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ciclosporin*:

| Supplier | Substance   | Batch     | Sample ID | Spectra | Certificate |
|----------|-------------|-----------|-----------|---------|-------------|
| Fagron   | Ciclosporin | 13D26-N07 | 20941     | 40      | 1402057     |
| Caelo    | Ciclosporin | 12317707  | 21082     | 40      | 20121119    |
| Caelo    | Ciclosporin | 13148604  | 21474     | 40      | 1412541     |
| Caelo    | Ciclosporin | 13148604  | 21475     | 40      | 20130613    |
| Fagron   | Ciclosporin | 13D26-N07 | 21671     | 40      | 1508429     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Ciclosporin*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 8 reference samples from the substance/substance group *Ciclosporin*.

| Supplier | Substance   | Batch            | Sample ID          | Spectra |
|----------|-------------|------------------|--------------------|---------|
| Fagron   | Ciclosporin | 10F22-N01        | 20232              | 40      |
| Fagron   | Ciclosporin | 10G07-N03        | 20281              | 40      |
| Caelo    | Ciclosporin | 13148604         | 21474 <sup>†</sup> | 20      |
| Caelo    | Ciclosporin | 13148604         | 21475 <sup>†</sup> | 20      |
| Fagron   | Ciclosporin | 13D26-N07        | 21671 <sup>†</sup> | 20      |
| Caelo    | Ciclosporin | 15278907         | 22966              | 40      |
| Fagron   | Ciclosporin | 16C09-B02-325955 | 23521              | 30      |
| Caelo    | Ciclosporin | 171583           | 23669              | 30      |

- 146 489 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 132 spectra from 54 *Apo-Ident* customers from 47 batches from the substance/substance group *Ciclosporin*.

| Supplier          | Substance   | Batch            | Spectra |
|-------------------|-------------|------------------|---------|
| Fagron            | Ciclosporin | 10J18-N06        | 1       |
| Caelo             | Ciclosporin | 13148604         | 1       |
| Caelo             | Ciclosporin | 13148606         | 7       |
| Caelo             | Ciclosporin | 13346803         | 5       |
| Caelo             | Ciclosporin | 13346808         | 1       |
| Fagron            | Ciclosporin | 13414038         | 5       |
| Fagron            | Ciclosporin | 13414092         | 3       |
| Fagron            | Ciclosporin | 13A28-N04        | 5       |
| Fagron            | Ciclosporin | 13B19-N02        | 3       |
| Fagron            | Ciclosporin | 13B19N02         | 2       |
| Caelo             | Ciclosporin | 13D26-N07        | 4       |
| Fagron            | Ciclosporin | 13D26-N07        | 8       |
| VDL               | Ciclosporin | 13D26-N07        | 1       |
| Fagron            | Ciclosporin | 13H19N09         | 1       |
| Fagron            | Ciclosporin | 13H19-N09        | 4       |
| Fagron            | Ciclosporin | 14/18-B02-300180 | 1       |
| Caelo             | Ciclosporin | 14199104         | 4       |
| Fagron            | Ciclosporin | 14718-b02-300180 | 1       |
| Fagron            | Ciclosporin | 14A15-N01        | 5       |
| Fagron            | Ciclosporin | 14a15-n01        | 1       |
| Fagron            | Ciclosporin | 14G22-B02-296891 | 5       |
| Caelo             | Ciclosporin | 15049703         | 3       |
| Caelo             | Ciclosporin | 15278901         | 3       |
| Caelo             | Ciclosporin | 15278902         | 2       |
| Fagron            | Ciclosporin | 15D23-B05        | 2       |
| Fagron            | Ciclosporin | 15D23-B05-307217 | 1       |
| Fagron            | Ciclosporin | 15D23-B05-308853 | 1       |
| Fagron            | Ciclosporin | 15f29-b14-316270 | 2       |
| Fagron            | Ciclosporin | 15F29B14316270   | 1       |
| Fagron            | Ciclosporin | 15f29-b14-325654 | 1       |
| Fagron            | Ciclosporin | 16121401         | 1       |
| Fagron            | Ciclosporin | 1103531          | 2       |
| Caelo             | Ciclosporin | 29689114C22B02   | 1       |
| Fagron            | Ciclosporin | 1110532          | 1       |
| Fagron            | Ciclosporin | 11K17-N13        | 1       |
| Caelo             | Ciclosporin | 12165602         | 3       |
| Caelo             | Ciclosporin | 12165603         | 2       |
| Caelo             | Ciclosporin | 123117702        | 1       |
| Caelo             | Ciclosporin | 12317702         | 6       |
| Caelo             | Ciclosporin | 12317703         | 1       |
| Caelo             | Ciclosporin | 12317707         | 4       |
| Caelo             | Ciclosporin | 12E31-N02        | 1       |
| Fagron            | Ciclosporin | 12E31-N02        | 9       |
| phönix 22.01.2013 | Ciclosporin | 12E31-N02        | 2       |
| Caelo             | Ciclosporin | 13031303         | 1       |
| Fagron            | Ciclosporin | 13A28-n04        | 1       |
| Anzag 23.03.13    | Ciclosporin | 13A28-N04        | 1       |
| Caelo             | Ciclosporin | 13A28-N04        | 4       |
| Phönix            | Ciclosporin | 13D26-N07        | 1       |
| Fargon            | Ciclosporin | 13D26-No7        | 1       |
| Fagron            | Ciclosporin | 25051302         | 1       |
| Caelo             | Ciclosporin | 14A15-No1        | 1       |
| Caelo             | Ciclosporin | 19011301         | 1       |
| Fagron            | Ciclosporin | 13d026N07        | 1       |

- 69 501 spectra from 414 *Apo-Ident* customers from a total of 23 754 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ciclosporin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ciclosporin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 200           | 0              | 71 186        |
| Type B | 0              | 198           | 42             | 146 489       |
| Type C | 0              | 103           | 29             | 69 501        |

The substance/substance group *Ciclosporin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 82.5000 % (> 81.2500 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 78.0303 % (> 75.7576 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20941     | 20941               | 0.00                         | 22.57                           |
| 21082     | 21474               | 10.16                        | 22.92                           |
| 21474     | 21474               | 0.00                         | 20.65                           |
| 21475     | 21474               | 1.97                         | 20.72                           |
| 21671     | 21671               | 0.00                         | 23.18                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das

alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Cinchocaine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20785-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Cinchocaine hydrochloride; Cinchocaini hydrochloridum; Cinchocainum hydrochloricum

### Special notes

When selecting the *Cinchocaine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cinchocaine hydrochloride*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------------|-----------|-----------|---------|-------------|
| Fagron   | Cinchocaine hydr... | 12F25-N10 | 20785     | 40      | 1401148     |
| Fagron   | Cinchocaine hydr... | 13G24-N05 | 21223     | 40      | 20130826    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Cinchocaine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 0 spectra of 0 reference samples from the substance/substance group *Cinchocaine hydrochloride*.
- 146 729 spectra from a total of 3194 batches from further 863 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 2 spectra from 2 *Apo-Ident* customers from 2 batches from the substance/substance group *Cinchocaine hydrochloride*.

| Supplier | Substance                 | Batch     | Spectra |
|----------|---------------------------|-----------|---------|
| Phönix   | Cinchocaine hydrochloride | 13E13-N07 | 1       |
| Fagron   | Cinchocaine hydrochloride | 12F25-N10 | 1       |

- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cinchocaine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cinchocaine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 0             | 0              | 146 729       |
| <b>Type C</b> | 0              | 1             | 1              | 69 631        |

The substance/substance group *Cinchocaine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | n/a (n/a)                |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20785     | 20785               | 0.00                         | 45.11                           |
| 21223     | 20785               | 7.66                         | 46.04                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Cinnarizine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20681-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Cinnarizine; Cinnarizinum

### Special notes

When selecting the *Cinnarizine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cinnarizine*:

| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate        |
|----------|-------------|------------------|-----------|---------|--------------------|
| Fagron   | Cinnarizine | 11L22-N13        | 20681     | 40      | 20120104           |
| Fagron   | Cinnarizine | 13H01-N07        | 20946     | 40      | 1402306            |
| Fagron   | Cinnarizine | 14D09-B01-294702 | 22358     | 40      | AR-16-FG-008930-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Cinnarizine*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *Cinnarizine*.

| Supplier | Substance   | Batch            | Sample ID          | Spectra |
|----------|-------------|------------------|--------------------|---------|
| Fagron   | Cinnarizine | 11L22-N13        | 20590              | 40      |
| Fagron   | Cinnarizine | 14D09-B01-294702 | 22358 <sup>†</sup> | 20      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 13 spectra from 3 *Apo-Ident* customers from 6 batches from the substance/substance group *Cinnarizine*.

| Supplier | Substance   | Batch     | Spectra |
|----------|-------------|-----------|---------|
| Fagron   | Cinnarizine | 8D11-N04  | 1       |
| Fagron   | Cinnarizine | 13H01-N07 | 4       |
| Fagron   | Cinnarizine | 13I26-N22 | 2       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

continued from previous page

| Supplier | Substance   | Batch            | Spectra |
|----------|-------------|------------------|---------|
| Fagron   | Cinnarizine | 14D09-B01        | 3       |
| Fagron   | Cinnarizine | 14D09-B01-292883 | 1       |
| Fagron   | Cinnarizine | 14D09-B01-294702 | 2       |

- 69 620 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cinnarizine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cinnarizine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 13            | 0              | 69 620        |

The substance/substance group *Cinnarizine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20681     | 22358               | 10.51                        | 64.70                           |
| 20946     | 20946               | 0.00                         | 66.42                           |
| 22358     | 22358               | 0.00                         | 65.78                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ciprofloxacin hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20945-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ciprofloxacin hydrochloride; Ciprofloxacin hydrochloridum

### Special notes

When selecting the *Ciprofloxacin hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ciprofloxacin hydrochloride*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------------|-----------|-----------|---------|-------------|
| Fagron   | Ciprofloxacin hy... | 12B08-N03 | 20945     | 40      | 1401421     |
| Fagron   | Ciprofloxacin hy... | 14B25-B02 | 21254     | 40      | 20140324    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Ciprofloxacin hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *Ciprofloxacin hydrochloride*.

| Supplier | Substance                   | Batch            | Sample ID | Spectra |
|----------|-----------------------------|------------------|-----------|---------|
| Fagron   | Ciprofloxacin hydrochloride | 15D07-B01-312864 | 22755     | 40      |
| Fagron   | Ciprofloxacin hydrochloride | 15D07-B01-312864 | 23568     | 40      |

- 146 649 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 6 spectra from 3 *Apo-Ident* customers from 6 batches from the substance/substance group *Ciprofloxacin hydrochloride*.

| Supplier | Substance                   | Batch             | Spectra |
|----------|-----------------------------|-------------------|---------|
| Fagron   | Ciprofloxacin hydrochloride | 13F13-N03         | 1       |
| Fagron   | Ciprofloxacin hydrochloride | 14/15-B08-303363  | 1       |
| Fagron   | Ciprofloxacin hydrochloride | 14B25-B02-291-783 | 1       |
| Fagron   | Ciprofloxacin hydrochloride | 14B25-B02-291783  | 1       |
| Fagron   | Ciprofloxacin hydrochloride | 14I15-B08         | 1       |
| Fagron   | Ciprofloxacin hydrochloride | 14I15-B08         | 1       |

- 69 627 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ciprofloxacin hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ciprofloxacin hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 6             | 0              | 69 627        |

The substance/substance group *Ciprofloxacin hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8815 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20945     | 20945               | 0.00                         | 46.30                           |
| 21254     | 20945               | 5.43                         | 48.45                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das

alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Citric acid monohydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20012-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Citric acid monohydrate; Acidum citricum monohydricum

### Special notes

When selecting the *Citric acid monohydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Citric acid monohydrate*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------------|-----------|-----------|---------|-------------|
| Fagron   | Citric acid mono... | 12D26-N02 | 20926     | 40      | 20120515    |
| Caelo    | Citric acid mono... | 15185301  | 22340     | 40      | 20150708    |
| Caelo    | Citric acid mono... | 161865    | 22617     | 40      | 20160706*   |
| Caelo    | Citric acid mono... | 17085602  | 23409     | 40      | 20170410    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Citric acid monohydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 170 spectra of 5 reference samples from the substance/substance group *Citric acid monohydrate*.

| Supplier | Substance               | Batch    | Sample ID          | Spectra |
|----------|-------------------------|----------|--------------------|---------|
| Caelo    | Citric acid monohydrate | 82803249 | 20012              | 30      |
| Caelo    | Citric acid monohydrate | 15185301 | 22340 <sup>†</sup> | 20      |
| Caelo    | Citric acid monohydrate | 161865   | 23298              | 40      |
| Hedinger | Citric acid monohydrate | 202029   | 23457              | 40      |
| Hedinger | Citric acid monohydrate | 202029   | 23458              | 40      |

- 146 559 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 164 spectra from 57 *Apo-Ident* customers from 59 batches from the substance/substance group *Citric acid monohydrate*.

| Supplier            | Substance               | Batch          | Spectra |
|---------------------|-------------------------|----------------|---------|
| Caelo               | Citric acid monohydrate | 13069105       | 3       |
| Caelo               | Citric acid monohydrate | 13069125       | 2       |
| Caelo               | Citric acid monohydrate | 13069133       | 5       |
| Caelo               | Citric acid monohydrate | 13069103       | 2       |
| Caelo               | Citric acid monohydrate | 14311807       | 3       |
| Caelo               | Citric acid monohydrate | 15087512       | 1       |
| Caelo               | Citric acid monohydrate | 15185304       | 11      |
| Caelo               | Citric acid monohydrate | 15185317       | 1       |
| Caelo               | Citric acid monohydrate | P135/14        | 1       |
| Caelo               | Citric acid monohydrate | 12125907       | 7       |
| Caelo               | Citric acid monohydrate | 13069104       | 6       |
| Caelo               | Citric acid monohydrate | 13069113       | 2       |
| Caelo               | Citric acid monohydrate | 12125937       | 3       |
| Caelo               | Citric acid monohydrate | 13069110       | 4       |
| Caelo               | Citric acid monohydrate | 13069111       | 4       |
| Caelo               | Citric acid monohydrate | 13069124       | 5       |
| Caelo               | Citric acid monohydrate | 13069128       | 4       |
| Caelo               | Citric acid monohydrate | 13069129       | 4       |
| Caelo               | Citric acid monohydrate | 13069130       | 1       |
| Caelo               | Citric acid monohydrate | 14038401       | 11      |
| Caelo               | Citric acid monohydrate | 14038403       | 7       |
| Caelo               | Citric acid monohydrate | 14311808       | 4       |
| Caelo               | Citric acid monohydrate | 14311812       | 4       |
| Caelo               | Citric acid monohydrate | 14311813       | 1       |
| Caelo               | Citric acid monohydrate | 15087502       | 3       |
| Caelo               | Citric acid monohydrate | 15087503       | 2       |
| Caelo               | Citric acid monohydrate | 15087509       | 8       |
| Caelo               | Citric acid monohydrate | 15087510       | 1       |
| Caelo               | Citric acid monohydrate | 15185301       | 2       |
| Caelo               | Citric acid monohydrate | 15185302       | 4       |
| Caelo               | Citric acid monohydrate | 2515Q-02959    | 1       |
| Bombastus           | Citric acid monohydrate | 287593         | 1       |
| Krieger             | Citric acid monohydrate | 613001-1-P     | 1       |
| Caelo               | Citric acid monohydrate | 15185309       | 1       |
| Caelo               | Citric acid monohydrate | 15185314       | 1       |
| Ebert 17.08.16      | Citric acid monohydrate | 15185314       | 1       |
| gepapharm GmbH      | Citric acid monohydrate | 15185314       | 2       |
| Caelo               | Citric acid monohydrate | 15185316       | 2       |
| Caelo               | Citric acid monohydrate | 15185321       | 2       |
| Caelo               | Citric acid monohydrate | 16186501       | 1       |
| Caelo               | Citric acid monohydrate | 16186502       | 1       |
| Bombastus           | Citric acid monohydrate | 259437         | 1       |
| VDL                 | Citric acid monohydrate | 263669         | 1       |
| Phönix              | Citric acid monohydrate | 10111503       | 2       |
| Caelo               | Citric acid monohydrate | 11208130       | 5       |
| Caelo               | Citric acid monohydrate | 11041413       | 1       |
| Caelo               | Citric acid monohydrate | 11208132       | 5       |
| Krämer&Martin       | Citric acid monohydrate | 11742009053020 | 1       |
| Caelo               | Citric acid monohydrate | 11208133       | 1       |
| Fagron              | Citric acid monohydrate | 11K01-N05      | 1       |
| Caelo               | Citric acid monohydrate | 12125904       | 2       |
| Caelo               | Citric acid monohydrate | 12125938       | 1       |
| Caesar &Loretz GmbH | Citric acid monohydrate | 12125937       | 1       |
| Caelo               | Citric acid monohydrate | 1212937        | 1       |
| Caelo               | Citric acid monohydrate | 1215907        | 1       |
| Caelo               | Citric acid monohydrate | 1215911        | 1       |

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| Supplier              | Substance               | Batch     | Spectra |
|-----------------------|-------------------------|-----------|---------|
| Sanacorp              | Citric acid monohydrate | 1215937   | 1       |
| Fagron                | Citric acid monohydrate | 12D26-N02 | 1       |
| Caelo                 | Citric acid monohydrate | 13069106  | 3       |
| Fiebig28.08.13 EK6,60 | Citric acid monohydrate | 13069111  | 1       |
| Caelo                 | Citric acid monohydrate | 13069126  | 1       |
| Caelo                 | Citric acid monohydrate | 1306915   | 1       |
| Azelis                | Citric acid monohydrate | TH4120517 | 1       |

- 69 469 spectra from 414 *Apo-Ident* customers from a total of 23 743 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Citric acid monohydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Citric acid monohydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 170           | 0              | 146 559       |
| <b>Type C</b> | 0              | 150           | 14             | 69 469        |

The substance/substance group *Citric acid monohydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.4706 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 91.4634 % (> 89.6341 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20926     | 22617               | 12.07                        | 54.42                           |
| 22340     | 22617               | 4.17                         | 53.24                           |
| 22617     | 22617               | 0.00                         | 53.25                           |
| 23409     | 22617               | 11.60                        | 54.86                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Citric acid, anhydrous</b>                                   |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20019-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Citric acid, anhydrous; Acidum citricum anhydricum

### Special notes

When selecting the *Citric acid, anhydrous* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Citric acid, anhydrous*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------------|-----------|-----------|---------|-------------|
| Caelo    | Citric acid, anh... | 11380204  | 20682     | 40      | 20120127    |
| Caelo    | Citric acid, anh... | 12043112  | 20683     | 40      | 20120229    |
| Fagron   | Citric acid, anh... | 12F18-N03 | 20706     | 40      | 20120628    |
| Fagron   | Citric acid, anh... | 13G24-N13 | 20913     | 40      | 20130827    |
| Caelo    | Citric acid, anh... | 13396502  | 21455     | 40      | 20140110    |
| Caelo    | Citric acid, anh... | 13243213  | 21487     | 40      | 20130821    |
| Caelo    | Citric acid, anh... | 160386    | 22463     | 40      | 20160315*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 280 spectra of 7 reference samples from the substance/substance group *Citric acid, anhydrous*. These samples are listed above in the [calibration samples](#) section.
- 71 106 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 410 spectra of 10 reference samples from the substance/substance group *Citric acid, anhydrous*.

| Supplier | Substance              | Batch    | Sample ID          | Spectra |
|----------|------------------------|----------|--------------------|---------|
| Caelo    | Citric acid, anhydrous | 91584259 | 20019              | 70      |
| Caelo    | Citric acid, anhydrous | 13396502 | 21455 <sup>†</sup> | 20      |
| Caelo    | Citric acid, anhydrous | 160386   | 22463 <sup>†</sup> | 20      |
| Caelo    | Citric acid, anhydrous | 160387   | 22478              | 60      |
| Caelo    | Citric acid, anhydrous | 162086   | 22620              | 40      |
| Caelo    | Citric acid, anhydrous | 162154   | 22622              | 40      |
| Caelo    | Citric acid, anhydrous | 171627   | 23303              | 40      |
| Caelo    | Citric acid, anhydrous | 171626   | 23421              | 40      |
| Caelo    | Citric acid, anhydrous | 171626   | 23648              | 40      |
| Caelo    | Citric acid, anhydrous | 171627   | 23677              | 40      |

- 146 319 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1341 spectra from 314 *Apo-Ident* customers from 370 batches from the substance/substance group *Citric acid, anhydrous*.

| Supplier                   | Substance              | Batch               | Spectra |
|----------------------------|------------------------|---------------------|---------|
| Noweda                     | Citric acid, anhydrous | 10182420            | 2       |
| Caelo                      | Citric acid, anhydrous |                     | 4       |
| Caelo                      | Citric acid, anhydrous | 13175403            | 19      |
| Caelo                      | Citric acid, anhydrous | 13243201            | 20      |
| Caelo                      | Citric acid, anhydrous | 13243213            | 21      |
| VDL;23.6.14; 2.49EUR       | Citric acid, anhydrous | 13243213            | 1       |
| Caelo                      | Citric acid, anhydrous | 13243214            | 16      |
| Caelo                      | Citric acid, anhydrous | 13243216            | 13      |
| Caelo                      | Citric acid, anhydrous | 13243218            | 8       |
| Caelo                      | Citric acid, anhydrous | 13243219            | 4       |
| Caelo                      | Citric acid, anhydrous | 13243224            | 2       |
| Caelo                      | Citric acid, anhydrous | 13243229            | 1       |
| Bombastus                  | Citric acid, anhydrous | 13396502            | 1       |
| Caelo                      | Citric acid, anhydrous | 13396506            | 1       |
| Caelo                      | Citric acid, anhydrous | 13396515            | 5       |
| Sanacorb;20.04.15; 7,45EUR | Citric acid, anhydrous | 1375410             | 1       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-291522    | 3       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-291519    | 5       |
| Caelo                      | Citric acid, anhydrous | 14186312            | 14      |
| Fagron                     | Citric acid, anhydrous | 14E06-B07-293890    | 3       |
| Caelo                      | Citric acid, anhydrous | 1506204             | 1       |
| Caelo                      | Citric acid, anhydrous | 15063003            | 11      |
| Caelo                      | Citric acid, anhydrous | 15063204            | 6       |
| Caelo                      | Citric acid, anhydrous | 15063213            | 16      |
| Caelo                      | Citric acid, anhydrous | 15087903            | 9       |
| Caelo                      | Citric acid, anhydrous | 16004701            | 11      |
| Caelo                      | Citric acid, anhydrous | 16004705            | 3       |
| Caelo                      | Citric acid, anhydrous | 16004706            | 8       |
| Caelo                      | Citric acid, anhydrous | 16038704            | 8       |
| Caelo                      | Citric acid, anhydrous | 16038607            | 2       |
| Euro OTC                   | Citric acid, anhydrous | L1408011-02         | 1       |
| Holdermann                 | Citric acid, anhydrous | 1011047-03          | 1       |
| Caelo                      | Citric acid, anhydrous | 10182420            | 1       |
| Caelo                      | Citric acid, anhydrous | 11380204            | 6       |
| Fagron                     | Citric acid, anhydrous | 1155609             | 15      |
| Gehe                       | Citric acid, anhydrous | 11F29-N03           | 1       |
| Fagron                     | Citric acid, anhydrous | 11K07-N01           | 10      |
| Caelo                      | Citric acid, anhydrous | 1155609             | 2       |
| Caelo                      | Citric acid, anhydrous | 12043111            | 1       |
| Caelo                      | Citric acid, anhydrous | 12043105            | 2       |
| Caelo                      | Citric acid, anhydrous | 12156824            | 12      |
| Sanacorp                   | Citric acid, anhydrous | 12156824            | 1       |
| Fagron                     | Citric acid, anhydrous | 12B01-N01           | 23      |
| Caelo                      | Citric acid, anhydrous | 12B01-N01           | 3       |
| Fagron                     | Citric acid, anhydrous | 12b01-N01           | 1       |
| Caelo                      | Citric acid, anhydrous | 13050617            | 13      |
| Caelo                      | Citric acid, anhydrous | 13050623-3376319052 | 1       |
| Fagron                     | Citric acid, anhydrous | 13A04N04            | 1       |
| Caelo                      | Citric acid, anhydrous | 13A04-N04           | 6       |
| EuRho/Phönix               | Citric acid, anhydrous | L1304042-01         | 1       |
| Caelo                      | Citric acid, anhydrous | 1072015B            | 1       |
| Fagron                     | Citric acid, anhydrous | 100614d             | 1       |

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| Supplier             | Substance              | Batch             | Spectra |
|----------------------|------------------------|-------------------|---------|
| Caelo                | Citric acid, anhydrous | 11178303          | 3       |
| Caelo                | Citric acid, anhydrous | 11380217          | 2       |
| Fagron               | Citric acid, anhydrous | 1156158           | 1       |
| Fagron               | Citric acid, anhydrous | 1172673           | 5       |
| Fagron               | Citric acid, anhydrous | 11C24N022869/4250 | 1       |
| Fagron               | Citric acid, anhydrous | 11H30-N05         | 2       |
| Caelo                | Citric acid, anhydrous | 12156811          | 13      |
| Caelo                | Citric acid, anhydrous | 12156832          | 9       |
| Caelo                | Citric acid, anhydrous | 12175708          | 3       |
| Caelo                | Citric acid, anhydrous | 12175711          | 5       |
| Caelo                | Citric acid, anhydrous | 12175716          | 4       |
| Caelo                | Citric acid, anhydrous | 12175718          | 1       |
| Caesar/Noweda        | Citric acid, anhydrous | 12B01-N01         | 2       |
| Caelo                | Citric acid, anhydrous | 13031502          | 1       |
| Caelo                | Citric acid, anhydrous | 13050611          | 6       |
| Caelo                | Citric acid, anhydrous | 13050622          | 10      |
| Caelo                | Citric acid, anhydrous | 13061502          | 1       |
| Caelo                | Citric acid, anhydrous | 1317504           | 1       |
| Caelo                | Citric acid, anhydrous | 13175404          | 6       |
| Caelo                | Citric acid, anhydrous | 13175405          | 9       |
| Caelo                | Citric acid, anhydrous | 13175406          | 3       |
| Caelo                | Citric acid, anhydrous | 13175409          | 23      |
| Caelo                | Citric acid, anhydrous | 13175410          | 4       |
| Caelo                | Citric acid, anhydrous | 13175411          | 12      |
| Caelo                | Citric acid, anhydrous | 13175426          | 6       |
| Caelo                | Citric acid, anhydrous | 13242225          | 1       |
| Caelo                | Citric acid, anhydrous | 13243005          | 1       |
| Caesar & Loretz GmbH | Citric acid, anhydrous | 13243201          | 1       |
| Caelo                | Citric acid, anhydrous | 13243202          | 11      |
| Caelo                | Citric acid, anhydrous | 13243208          | 2       |
| Caelo                | Citric acid, anhydrous | 13243210          | 8       |
| Gehe                 | Citric acid, anhydrous | 13243213          | 1       |
| Sanacorp             | Citric acid, anhydrous | 13243214          | 1       |
| Caesar & Loretz GmbH | Citric acid, anhydrous | 13243214          | 1       |
| Caelo                | Citric acid, anhydrous | 13243217          | 7       |
| GEHE 02.07.2014      | Citric acid, anhydrous | 13243217          | 1       |
| Caelo                | Citric acid, anhydrous | 13243220          | 2       |
| Caelo                | Citric acid, anhydrous | 13243221          | 9       |
| Caelo                | Citric acid, anhydrous | 13243222          | 2       |
| Caelo                | Citric acid, anhydrous | 13243225          | 5       |
| Caelo                | Citric acid, anhydrous | 13396502          | 4       |
| AHD                  | Citric acid, anhydrous | 13396502          | 1       |
| Caelo                | Citric acid, anhydrous | 13396504          | 3       |
| Caelo                | Citric acid, anhydrous | 13396505          | 1       |
| Phoenix 07.04.2014   | Citric acid, anhydrous | 13A04-N04         | 1       |
| Fagron               | Citric acid, anhydrous | 13A04-N04         | 13      |
| Phönix Gotha         | Citric acid, anhydrous | 13A04-N040049-100 | 1       |
| Caelo                | Citric acid, anhydrous | 13D29-N02         | 1       |
| Fagron               | Citric acid, anhydrous | 13D29N02          | 1       |
| Fagron               | Citric acid, anhydrous | 13F12-N08         | 2       |
| Fagron               | Citric acid, anhydrous | 13F12-N01         | 3       |
| Fagron               | Citric acid, anhydrous | 13G04-N05         | 6       |
| Caelo                | Citric acid, anhydrous | 13G24N13          | 2       |
| Fagron               | Citric acid, anhydrous | 13G24-N24         | 11      |
| Fagron               | Citric acid, anhydrous | 13G24-N240029/900 | 1       |
| Fagron               | Citric acid, anhydrous | 13G24-N240739/900 | 1       |
| Fagron               | Citric acid, anhydrous | 13H22-N09         | 2       |
| Fagron               | Citric acid, anhydrous | 13K18-B34         | 8       |
| Caelo                | Citric acid, anhydrous | 13K18-B34         | 1       |
| Fagron               | Citric acid, anhydrous | 13K18-B34-288371  | 4       |

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| Supplier                   | Substance              | Batch                | Spectra |
|----------------------------|------------------------|----------------------|---------|
| Caelo                      | Citric acid, anhydrous | 13K18-B34-288371TEST | 1       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-288372     | 7       |
| Caelo                      | Citric acid, anhydrous | 13K18-B34-288372     | 1       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-288372     | 1       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-288373     | 2       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-291071     | 4       |
| Großhandel                 | Citric acid, anhydrous | 13K18-B34-291072     | 1       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-291072     | 1       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-291520     | 6       |
| Fagron                     | Citric acid, anhydrous | 13K18B34291520       | 1       |
| Caelo                      | Citric acid, anhydrous | 13K18-B34-291520     | 1       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-291521     | 4       |
| Caelo                      | Citric acid, anhydrous | 13K18-B34-291522     | 1       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-291523     | 1       |
| Fagron                     | Citric acid, anhydrous | 13K18-b34-291522     | 1       |
| Caelo                      | Citric acid, anhydrous | 13K18-B34-291523     | 2       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34-293871     | 2       |
| Fagron                     | Citric acid, anhydrous | 13L05-B02-296246     | 3       |
| Fagron                     | Citric acid, anhydrous | 13L05-B02-309050     | 1       |
| Fagron                     | Citric acid, anhydrous | 13L18-B39-289347     | 4       |
| Caelo                      | Citric acid, anhydrous | 14041506             | 1       |
| Caelo                      | Citric acid, anhydrous | 14071501             | 1       |
| Caelo                      | Citric acid, anhydrous | 14186301             | 16      |
| Cealo/Gehe                 | Citric acid, anhydrous | 14186301             | 6       |
| Caelo                      | Citric acid, anhydrous | 14186302             | 11      |
| Phönix                     | Citric acid, anhydrous | 14186312             | 4       |
| Caelo                      | Citric acid, anhydrous | 14186313             | 4       |
| Caelo                      | Citric acid, anhydrous | 14186314             | 3       |
| Caelo                      | Citric acid, anhydrous | 14E06-B07            | 1       |
| Fagron                     | Citric acid, anhydrous | 14E06-B07            | 1       |
| Fagron                     | Citric acid, anhydrous | 14E06-B07293872      | 1       |
| Gehe Kassel, 22.05.2015    | Citric acid, anhydrous | 14E06-B07-293872     | 1       |
| Fagron                     | Citric acid, anhydrous | 14E06-B07-293872     | 3       |
| Caelo                      | Citric acid, anhydrous | 14E06-B07-293873     | 1       |
| Fagron                     | Citric acid, anhydrous | 14E06-B07-293875     | 2       |
| Fagron                     | Citric acid, anhydrous | 14E06-B07-29389      | 1       |
| Fagron                     | Citric acid, anhydrous | 14G04-B09-293874     | 9       |
| Caelo                      | Citric acid, anhydrous | 14G04-B09-293876     | 3       |
| Fagron                     | Citric acid, anhydrous | 14G04B09296361       | 1       |
| Fagron                     | Citric acid, anhydrous | 14K05-B04-302816     | 5       |
| Caelo                      | Citric acid, anhydrous | 15044901             | 6       |
| Fagron                     | Citric acid, anhydrous | 14G04B09293876       | 1       |
| Caelo                      | Citric acid, anhydrous | 15044902             | 3       |
| Fagron                     | Citric acid, anhydrous | 15044902             | 1       |
| Caelo                      | Citric acid, anhydrous | 15044903             | 5       |
| Caeolo/Gehe                | Citric acid, anhydrous | 15044903             | 3       |
| Caelo                      | Citric acid, anhydrous | 15044904             | 6       |
| Caelo                      | Citric acid, anhydrous | 15044905             | 4       |
| Caelo                      | Citric acid, anhydrous | 15063001             | 1       |
| Caesar & Loretz GmbH Hi... | Citric acid, anhydrous | 15063003             | 1       |
| Caesar & Loretz GmbH       | Citric acid, anhydrous | 15063003             | 2       |
| Caelo                      | Citric acid, anhydrous | 15063006             | 3       |
| Caelo                      | Citric acid, anhydrous | 15063203             | 9       |
| Caelo                      | Citric acid, anhydrous | 15063205             | 2       |
| Caelo                      | Citric acid, anhydrous | 15063206             | 14      |
| Caelo                      | Citric acid, anhydrous | 15063211             | 3       |
| AHD                        | Citric acid, anhydrous | 15063218             | 1       |
| Caelo                      | Citric acid, anhydrous | 15087510             | 1       |
| Caelo                      | Citric acid, anhydrous | 15087902             | 3       |
| Caelo                      | Citric acid, anhydrous | 15088016             | 2       |

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| <b>Supplier</b>            | <b>Substance</b>       | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------------|------------------|----------------|
| Caelo                      | Citric acid, anhydrous | 15124301         | 7              |
| Caelo                      | Citric acid, anhydrous | 15124303         | 2              |
| Caelo                      | Citric acid, anhydrous | 16004702         | 10             |
| Caesar&Loretz GmbH,16.0... | Citric acid, anhydrous | 16004706         | 1              |
| Caelo                      | Citric acid, anhydrous | 1604701          | 1              |
| Fagron                     | Citric acid, anhydrous | 16072014B        | 1              |
| Caelo                      | Citric acid, anhydrous | 16208607         | 5              |
| Fagron                     | Citric acid, anhydrous | 1714Q1024        | 1              |
| Caelo                      | Citric acid, anhydrous | 18091409         | 1              |
| Caelo                      | Citric acid, anhydrous | 28051401         | 1              |
| Sanacorp                   | Citric acid, anhydrous | 41/AKD4          | 1              |
| Caelo                      | Citric acid, anhydrous | 42/AKD1          | 1              |
| Phönix                     | Citric acid, anhydrous | 43/AKD13         | 1              |
| Fischar                    | Citric acid, anhydrous | 6493071          | 1              |
| Fischar/Noweda             | Citric acid, anhydrous | 6493051          | 1              |
| Otto Fischer / Sana        | Citric acid, anhydrous | 6493071          | 1              |
| Phoenix 07.04.2014         | Citric acid, anhydrous | 700309-0003      | 1              |
| Euro OTC                   | Citric acid, anhydrous | 702260           | 1              |
| Fagron                     | Citric acid, anhydrous | 700309-0003      | 2              |
| Euro OTC                   | Citric acid, anhydrous | L1408011-01      | 1              |
| Euro OTC                   | Citric acid, anhydrous | L1202001-02      | 1              |
| Euro OTC                   | Citric acid, anhydrous | L1503027-01      | 1              |
| EuRho                      | Citric acid, anhydrous | L1503027-02      | 2              |
| Euro OTC                   | Citric acid, anhydrous | L1503027-02      | 1              |
| Euro OTC                   | Citric acid, anhydrous | L1508013-01      | 2              |
| Caelo                      | Citric acid, anhydrous | 1015U-01024      | 1              |
| Caelo                      | Citric acid, anhydrous | 1396505          | 1              |
| Fagron                     | Citric acid, anhydrous | 13L05B02296247   | 1              |
| Caelo                      | Citric acid, anhydrous | 14G04B09293877   | 1              |
| Fagron                     | Citric acid, anhydrous | 14G04-B09-293876 | 1              |
| Fagron                     | Citric acid, anhydrous | 14G04-B09-293877 | 5              |
| Fagron                     | Citric acid, anhydrous | 14G04-B09-309707 | 1              |
| Fagron                     | Citric acid, anhydrous | 14G04-B09-309836 | 1              |
| Fagron                     | Citric acid, anhydrous | 14K05-B04-302815 | 2              |
| Caelo                      | Citric acid, anhydrous | 14K05-B04-302815 | 1              |
| Fagron                     | Citric acid, anhydrous | 14k05-b04-302816 | 1              |
| Fagron                     | Citric acid, anhydrous | 14K05-B04-302817 | 1              |
| Caelo                      | Citric acid, anhydrous | 1501-B06-324348  | 1              |
| Ebert & Jacobi 12.07...    | Citric acid, anhydrous | 1506214          | 1              |
| Jenne                      | Citric acid, anhydrous | 15063002         | 1              |
| Noweda                     | Citric acid, anhydrous | 15063203         | 1              |
| Caesar&Loretz GmbH         | Citric acid, anhydrous | 15063213         | 1              |
| Caelo                      | Citric acid, anhydrous | 15063214         | 5              |
| Caelo                      | Citric acid, anhydrous | 15063217         | 3              |
| Caelo                      | Citric acid, anhydrous | 15063218         | 6              |
| Noweda                     | Citric acid, anhydrous | 15087902         | 2              |
| Caesar & Loretz            | Citric acid, anhydrous | 15087904         | 2              |
| Caelo                      | Citric acid, anhydrous | 15088008         | 1              |
| 12.12.2016 Phoenix 4,59EUR | Citric acid, anhydrous | 15088008         | 1              |
| Caelo                      | Citric acid, anhydrous | 15088017         | 2              |
| Phoenix 12.12.2016 4,59EUR | Citric acid, anhydrous | 1508808          | 1              |
| Fagron                     | Citric acid, anhydrous | 15G16-B01        | 1              |
| Fagron                     | Citric acid, anhydrous | 15G16B01         | 1              |
| Fragron/Noweda             | Citric acid, anhydrous | 15G16-B01-330449 | 1              |
| Fagron                     | Citric acid, anhydrous | 15G16-B01-330450 | 3              |
| Fagron                     | Citric acid, anhydrous | 15G16B01330450   | 1              |
| Noweda                     | Citric acid, anhydrous | 16004701         | 1              |
| Caesar & Lorenz GmbH       | Citric acid, anhydrous | 16004706         | 1              |
| Caelo                      | Citric acid, anhydrous | 16038602         | 3              |
| Caelo                      | Citric acid, anhydrous | 16038603         | 2              |

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| Supplier            | Substance              | Batch       | Spectra |
|---------------------|------------------------|-------------|---------|
| Caelo               | Citric acid, anhydrous | 16038604    | 6       |
| Caelo               | Citric acid, anhydrous | 16038606    | 7       |
| Krieger             | Citric acid, anhydrous | 16038606    | 1       |
| Caelo               | Citric acid, anhydrous | 16038608    | 8       |
| Caelo               | Citric acid, anhydrous | 16038613    | 4       |
| Caelo               | Citric acid, anhydrous | 16038621    | 7       |
| Caelo               | Citric acid, anhydrous | 16038622    | 2       |
| Caelo               | Citric acid, anhydrous | 16038701    | 1       |
| Caelo/AHD           | Citric acid, anhydrous | 16038704    | 1       |
| Caelo               | Citric acid, anhydrous | 16038707    | 5       |
| Caelo               | Citric acid, anhydrous | 16038708    | 2       |
| Caelo               | Citric acid, anhydrous | 16038709    | 2       |
| Caelo               | Citric acid, anhydrous | 16208605    | 3       |
| Caelo               | Citric acid, anhydrous | 16208405    | 1       |
| Caelo               | Citric acid, anhydrous | 16208606    | 5       |
| Ebert-Jacobi        | Citric acid, anhydrous | 16208607    | 1       |
| Caelo               | Citric acid, anhydrous | 16208608    | 1       |
| Caelo               | Citric acid, anhydrous | 21531       | 1       |
| Caelo               | Citric acid, anhydrous | 16208610    | 2       |
| Fagron              | Citric acid, anhydrous | 330449      | 1       |
| fishar              | Citric acid, anhydrous | 6494061     | 1       |
| Otto Fischar        | Citric acid, anhydrous | 6494061     | 1       |
| Euro OTC            | Citric acid, anhydrous | L1604061-02 | 1       |
| Euro OTC            | Citric acid, anhydrous | L1609021-01 | 1       |
| Caelo               | Citric acid, anhydrous | xxxx        | 1       |
| Caelo               | Citric acid, anhydrous | xxxxxx      | 1       |
| Caelo               | Citric acid, anhydrous | 1081203     | 1       |
| Caelo               | Citric acid, anhydrous | 2071303     | 1       |
| Fagron              | Citric acid, anhydrous | 214U-01024  | 1       |
| Caelo               | Citric acid, anhydrous | 713I-01024  | 1       |
| Caelo               | Citric acid, anhydrous | 9158408     | 1       |
| Caelo               | Citric acid, anhydrous | 9199105     | 1       |
| Anzag               | Citric acid, anhydrous | 10049712    | 1       |
| Anzag               | Citric acid, anhydrous | 10049713    | 1       |
| Caelo               | Citric acid, anhydrous | 10049716    | 1       |
| Caelo               | Citric acid, anhydrous | 10109202    | 1       |
| Euro OTC            | Citric acid, anhydrous | 1011047-01  | 1       |
| Noweda              | Citric acid, anhydrous | 1011047-02  | 1       |
| Caelo               | Citric acid, anhydrous | 1011047-03  | 1       |
| Euro OTC            | Citric acid, anhydrous | 1011047-03  | 1       |
| Caelo               | Citric acid, anhydrous | 10182417    | 1       |
| Caelo               | Citric acid, anhydrous | 10182419    | 1       |
| Fagron              | Citric acid, anhydrous | 10G21-N05   | 1       |
| Caelo               | Citric acid, anhydrous | 11025514    | 1       |
| Caelo               | Citric acid, anhydrous | 11011310    | 1       |
| Caelo               | Citric acid, anhydrous | 11041410    | 1       |
| Caelo               | Citric acid, anhydrous | 11066805    | 1       |
| Caelo               | Citric acid, anhydrous | 11066806    | 1       |
| Caelo               | Citric acid, anhydrous | 11126901    | 1       |
| Anzag am 04.06.2012 | Citric acid, anhydrous | 11126901    | 1       |
| Caelo               | Citric acid, anhydrous | 11126904    | 1       |
| Caelo               | Citric acid, anhydrous | 11126909    | 1       |
| Caelo               | Citric acid, anhydrous | 11126911    | 1       |
| Caelo               | Citric acid, anhydrous | 11159801    | 2       |
| Caelo               | Citric acid, anhydrous | 11159816    | 1       |
| Caelo               | Citric acid, anhydrous | 11159817    | 4       |
| Caelo               | Citric acid, anhydrous | 11159821    | 3       |
| Caelo               | Citric acid, anhydrous | 11159824    | 1       |
| Caelo               | Citric acid, anhydrous | 11189817    | 1       |
| Fagron              | Citric acid, anhydrous | 1137408     | 2       |

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| Supplier                   | Substance              | Batch     | Spectra |
|----------------------------|------------------------|-----------|---------|
| Caelo                      | Citric acid, anhydrous | 113802013 | 1       |
| Caelo                      | Citric acid, anhydrous | 11380206  | 1       |
| Post-Apotheke              | Citric acid, anhydrous | 11380207  | 1       |
| Caelo                      | Citric acid, anhydrous | 11380208  | 1       |
| Caelo                      | Citric acid, anhydrous | 11380212  | 1       |
| Caelo                      | Citric acid, anhydrous | 11380213  | 1       |
| Caelo                      | Citric acid, anhydrous | 11380215  | 5       |
| Noweda                     | Citric acid, anhydrous | 1141364   | 1       |
| Fagron                     | Citric acid, anhydrous | 1141664   | 1       |
| Fagron                     | Citric acid, anhydrous | 1151608   | 3       |
| Gehe 04.04.2013            | Citric acid, anhydrous | 1155609   | 1       |
| Jungbunzlauer Ladenburg... | Citric acid, anhydrous | 1155609   | 1       |
| Jungbunzlauer Ladenburg... | Citric acid, anhydrous | 1156158   | 1       |
| Caelo                      | Citric acid, anhydrous | 1172673   | 1       |
| Fagron                     | Citric acid, anhydrous | 1181765   | 2       |
| Fagron                     | Citric acid, anhydrous | 11B11-N16 | 1       |
| GEHE                       | Citric acid, anhydrous | 11B11-N16 | 1       |
| Gehe                       | Citric acid, anhydrous | 11C24-N03 | 2       |
| Fagron                     | Citric acid, anhydrous | 11C24-N02 | 3       |
| Gehe                       | Citric acid, anhydrous | 11C24-N02 | 1       |
| Caelo                      | Citric acid, anhydrous | 11C24-N02 | 1       |
| Fagron                     | Citric acid, anhydrous | 11C24-N03 | 6       |
| Anzag 15.09.2012           | Citric acid, anhydrous | 11C24-N03 | 2       |
| Fagron                     | Citric acid, anhydrous | 11C24-N02 | 1       |
| Caelo                      | Citric acid, anhydrous | 11C24-N03 | 1       |
| Noweda                     | Citric acid, anhydrous | 11F29-N03 | 1       |
| Fagron                     | Citric acid, anhydrous | 11F29-N03 | 1       |
| Phönix Gotha               | Citric acid, anhydrous | 11K07-N01 | 1       |
| Caelo                      | Citric acid, anhydrous | 11K07-N01 | 1       |
| Fagron                     | Citric acid, anhydrous | 11K07N01  | 1       |
| Gehe                       | Citric acid, anhydrous | 11K07-N01 | 2       |
| Anzag, 19.12.2012          | Citric acid, anhydrous | 11K07-N01 | 1       |
| Caelo                      | Citric acid, anhydrous | 11K11-N02 | 1       |
| Fagron                     | Citric acid, anhydrous | 11K11-N02 | 2       |
| Caelo                      | Citric acid, anhydrous | 12043101  | 1       |
| ANZAG am 12.06.2012        | Citric acid, anhydrous | 12043104  | 1       |
| Noweda                     | Citric acid, anhydrous | 12043105  | 1       |
| Caelo                      | Citric acid, anhydrous | 12043109  | 1       |
| Caelo                      | Citric acid, anhydrous | 12043110  | 3       |
| Noweda                     | Citric acid, anhydrous | 12043110  | 2       |
| Gehe                       | Citric acid, anhydrous | 12043111  | 1       |
| Kehr                       | Citric acid, anhydrous | 12043112  | 1       |
| Caelo                      | Citric acid, anhydrous | 12043112  | 6       |
| Caelo                      | Citric acid, anhydrous | 12043113  | 8       |
| Caelo                      | Citric acid, anhydrous | 12043114  | 2       |
| Caelo                      | Citric acid, anhydrous | 12043118  | 5       |
| Caelo                      | Citric acid, anhydrous | 12043120  | 5       |
| Caelo                      | Citric acid, anhydrous | 12043123  | 9       |
| Alliance Healthcare        | Citric acid, anhydrous | 12043123  | 1       |
| Caelo                      | Citric acid, anhydrous | 12043124  | 3       |
| Caelo                      | Citric acid, anhydrous | 12156801  | 2       |
| Caelo                      | Citric acid, anhydrous | 12156803  | 8       |
| Caelo                      | Citric acid, anhydrous | 12156804  | 4       |
| Sanacorp                   | Citric acid, anhydrous | 12156811  | 1       |
| Finze                      | Citric acid, anhydrous | 12156812  | 2       |
| Caelo                      | Citric acid, anhydrous | 12156812  | 4       |
| Caesar & Loretz/ Noweda    | Citric acid, anhydrous | 12156812  | 1       |
| Caelo                      | Citric acid, anhydrous | 12156822  | 7       |
| Caelo                      | Citric acid, anhydrous | 12156823  | 5       |
| Sanacorp                   | Citric acid, anhydrous | 12156823  | 1       |

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| Supplier                   | Substance              | Batch              | Spectra |
|----------------------------|------------------------|--------------------|---------|
| Caelo                      | Citric acid, anhydrous | 12156830           | 1       |
| Sanacorp                   | Citric acid, anhydrous | 12156832           | 1       |
| Caelo                      | Citric acid, anhydrous | 121568704          | 1       |
| Sanacorp                   | Citric acid, anhydrous | 1216832            | 1       |
| Caelo                      | Citric acid, anhydrous | 12175709           | 1       |
| Fagron                     | Citric acid, anhydrous | 12801-N01          | 1       |
| Fagron                     | Citric acid, anhydrous | 12A20-N03          | 1       |
| Phoenix 13.02.13           | Citric acid, anhydrous | 12B01-N01          | 2       |
| Krömpke                    | Citric acid, anhydrous | 12B01-N01          | 2       |
| Fargon                     | Citric acid, anhydrous | 12B01-N01          | 1       |
| Großhandel                 | Citric acid, anhydrous | 12B01-N01          | 2       |
| Phoenix                    | Citric acid, anhydrous | 12b01-N01          | 1       |
| Phönix Gotha               | Citric acid, anhydrous | 12B01-N011973/6000 | 1       |
| Phönix Gotha               | Citric acid, anhydrous | 12B01-N012028/6000 | 1       |
| Gehe                       | Citric acid, anhydrous |                    | 1       |
| Fargon                     | Citric acid, anhydrous | 12B01-NN01         | 1       |
| Fagron                     | Citric acid, anhydrous | 12B01-N01          | 1       |
| Fagron                     | Citric acid, anhydrous | 12B01-No1          | 1       |
| Fagron                     | Citric acid, anhydrous | 12B01-N01          | 1       |
| Caelo                      | Citric acid, anhydrous | 12F06-M06          | 1       |
| Fagron                     | Citric acid, anhydrous | 12F06-M06          | 3       |
| Caelo                      | Citric acid, anhydrous | 13050601           | 9       |
| Noweda                     | Citric acid, anhydrous | 13050601           | 1       |
| Caesar & Loretz GmbH Hi... | Citric acid, anhydrous | 13050601           | 2       |
| Caelo                      | Citric acid, anhydrous | 13050604           | 15      |
| A.H. 08.06.13 ek: 6,92EUR  | Citric acid, anhydrous | 13050604           | 1       |
| Sanacorp                   | Citric acid, anhydrous | 13050604           | 2       |
| Caelo                      | Citric acid, anhydrous | 13050606           | 6       |
| Caelo                      | Citric acid, anhydrous | 13050607           | 10      |
| AHD                        | Citric acid, anhydrous | 13050607           | 1       |
| Phönix Gotha               | Citric acid, anhydrous | 13050609           | 1       |
| Caelo                      | Citric acid, anhydrous | 13050610           | 5       |
| Caesar/Lorenz              | Citric acid, anhydrous | 13050610           | 1       |
| 10; 26.06.2013             | Citric acid, anhydrous | 13050611           | 1       |
| Caelo                      | Citric acid, anhydrous | 13050613           | 16      |
| Caelo                      | Citric acid, anhydrous | 13050614           | 8       |
| Phoenix                    | Citric acid, anhydrous | 13050614           | 1       |
| 20; 10.07.2013             | Citric acid, anhydrous | 13050617           | 1       |
| Caelo                      | Citric acid, anhydrous | 13050618           | 3       |
| Caelo                      | Citric acid, anhydrous | 13050621           | 2       |
| Noweda                     | Citric acid, anhydrous | 13050621           | 1       |
| Caelo                      | Citric acid, anhydrous | 13050623           | 2       |
| Caelo                      | Citric acid, anhydrous | 13050624           | 1       |
| Caelo                      | Citric acid, anhydrous | 1305601            | 1       |
| Caelo                      | Citric acid, anhydrous | 13157404           | 1       |
| Caelo                      | Citric acid, anhydrous | 13175402           | 3       |
| Gehe                       | Citric acid, anhydrous | 13175403           | 1       |
| Gehe                       | Citric acid, anhydrous | 13175404           | 1       |
| Caelo                      | Citric acid, anhydrous | 13175414           | 2       |
| Caesar&lorenz,Phoenix      | Citric acid, anhydrous | 13243201           | 1       |
| Phoenix                    | Citric acid, anhydrous | 13243202           | 1       |
| Hustadt Apotheke           | Citric acid, anhydrous | 1350601            | 1       |
| Caelo                      | Citric acid, anhydrous | 1380208            | 1       |
| Caelo                      | Citric acid, anhydrous | 13804-N01          | 1       |
| Fagron                     | Citric acid, anhydrous | 13804-N02          | 1       |
| Fagron                     | Citric acid, anhydrous | 13A-04-N04         | 2       |
| Phönix                     | Citric acid, anhydrous | 13A04-N04          | 1       |
| Fagron                     | Citric acid, anhydrous | 13A04-N04          | 1       |
| Fagron                     | Citric acid, anhydrous | 13Ao4-No4          | 1       |
| Fagron                     | Citric acid, anhydrous | 13B04-N01          | 1       |

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| Supplier                   | Substance              | Batch              | Spectra |
|----------------------------|------------------------|--------------------|---------|
| Caelo                      | Citric acid, anhydrous | 13G24-N13          | 2       |
| Fagron                     | Citric acid, anhydrous | 13G24-N13          | 7       |
| Euro OTC                   | Citric acid, anhydrous | 13K18-B34          | 1       |
| Phoenix                    | Citric acid, anhydrous | 13K18-B34-288372   | 1       |
| Sanacorp                   | Citric acid, anhydrous | 13K18-B34-291072   | 1       |
|                            | Citric acid, anhydrous | 13K18-B34-291523   | 1       |
| Caelo                      | Citric acid, anhydrous | 15214301           | 1       |
| Fagron                     | Citric acid, anhydrous | 1601311024         | 1       |
| Caelo                      | Citric acid, anhydrous | 17071301           | 1       |
| Caelo                      | Citric acid, anhydrous | 19041304           | 1       |
| Caelo                      | Citric acid, anhydrous | 19041305           | 1       |
| Fagron                     | Citric acid, anhydrous | 1913A-01024        | 1       |
| Caelo                      | Citric acid, anhydrous | 20060912-3         | 1       |
| Fagron                     | Citric acid, anhydrous | 20071203           | 1       |
| Caelo                      | Citric acid, anhydrous | 20151112-1         | 1       |
| Fagron                     | Citric acid, anhydrous | 26082013B          | 1       |
| Fagron/Sanacorp            | Citric acid, anhydrous |                    | 1       |
| Fagron                     | Citric acid, anhydrous | 4810E-01024        | 1       |
| Otto Fischer GmbH          | Citric acid, anhydrous | 6492061            | 1       |
| ALLIANCE HEALTHCARE/FIS... | Citric acid, anhydrous | 6492061            | 1       |
| GEHE                       | Citric acid, anhydrous | 700309-0003        | 1       |
| Fagron                     | Citric acid, anhydrous | 700309-0006        | 1       |
| Fagron                     | Citric acid, anhydrous | 700309-001         | 1       |
| Caelo                      | Citric acid, anhydrous | A-040513-1         | 1       |
| Caelo                      | Citric acid, anhydrous | CH12043112         | 1       |
| Euro OTC                   | Citric acid, anhydrous | L1202001-01        | 5       |
| Eu Rho                     | Citric acid, anhydrous | L1202001-01        | 1       |
| Noweda                     | Citric acid, anhydrous | L1202001-02        | 1       |
| Euro OTC                   | Citric acid, anhydrous |                    | 1       |
| Euro OTC                   | Citric acid, anhydrous | L130404201         | 2       |
| Caelo                      | Citric acid, anhydrous | L130404202         | 1       |
| Euro OTC                   | Citric acid, anhydrous | L1304042-02        | 1       |
| Fagron                     | Citric acid, anhydrous | probe              | 1       |
| Phoenix                    | Citric acid, anhydrous | 1172673            | 1       |
| Fagron                     | Citric acid, anhydrous | 11K11-N020444/1975 | 1       |
| Fagron                     | Citric acid, anhydrous | 12175711           | 1       |
| Caelo                      | Citric acid, anhydrous | 133243218          | 1       |
| Alliance Health 03.06.2... | Citric acid, anhydrous | 13K18-B34          | 1       |
| Fagron                     | Citric acid, anhydrous | 13K18-B34291522    | 1       |
| Euro OTC                   | Citric acid, anhydrous | 1406014-02         | 1       |
| Fagron                     | Citric acid, anhydrous | 14E-06-B07-293890  | 1       |
| Fragon/Phoenix             | Citric acid, anhydrous | 14G04-B09-293976   | 1       |
| Lamotte                    | Citric acid, anhydrous | 15063213           | 1       |
| Caelo                      | Citric acid, anhydrous | 15091401           | 1       |
| Caelo                      | Citric acid, anhydrous | 1512402            | 1       |
| Caelo                      | Citric acid, anhydrous | 16038710           | 2       |
| Caelo                      | Citric acid, anhydrous | 16208613           | 1       |
| Caelo                      | Citric acid, anhydrous | 24021502           | 1       |
| Caelo                      | Citric acid, anhydrous | 11380205           | 1       |
| Sanacorp                   | Citric acid, anhydrous | 40/AKD2            | 1       |
| Caelo                      | Citric acid, anhydrous | 261BE-01024        | 1       |
| Fagron                     | Citric acid, anhydrous | 10G21-N05          | 2       |
| Caelo                      | Citric acid, anhydrous | 11178304           | 1       |
| Phönix                     | Citric acid, anhydrous | 1155609            | 1       |
| GEHE                       | Citric acid, anhydrous | 11C24-N03          | 1       |
| Caelo                      | Citric acid, anhydrous | 12043119           | 1       |
| Caelo                      | Citric acid, anhydrous | 12156818           | 1       |
| Caelo                      | Citric acid, anhydrous | 12156827           | 1       |
| Caelo                      | Citric acid, anhydrous | 12B01No1           | 1       |
| Phönix Gotha               | Citric acid, anhydrous | 12B01-N012125/6000 | 1       |

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continued from previous page

| Supplier      | Substance              | Batch              | Spectra |
|---------------|------------------------|--------------------|---------|
| Euro OTC      | Citric acid, anhydrous | 13050604           | 1       |
| Phoenix Gotha | Citric acid, anhydrous | 13050618           | 1       |
| Euro OTC      | Citric acid, anhydrous | 13175410           | 1       |
| fargon        | Citric acid, anhydrous | 13A04-N04          | 1       |
| Fagron        | Citric acid, anhydrous | 13A04-N040019/4900 | 1       |
| Fagron        | Citric acid, anhydrous | 22031401           | 1       |
| Caelo         | Citric acid, anhydrous | 26111301           | 1       |
| Caelo         | Citric acid, anhydrous | 27091303           | 1       |
| Caelo         | Citric acid, anhydrous | 27091304           | 1       |
| Fagron        | Citric acid, anhydrous | 28021404           | 1       |
| Caelo         | Citric acid, anhydrous | 28021405           | 1       |

- 68 292 spectra from 414 *Apo-Ident* customers from a total of 23 436 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Citric acid, anhydrous* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Citric acid, anhydrous* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 280           | 0              | 71 106        |
| <b>Type B</b> | 0              | 401           | 9              | 146 319       |
| <b>Type C</b> | 0              | 1330          | 11             | 68 292        |

The substance/substance group *Citric acid, anhydrous* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.8571 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 97.8049 % (> 97.0732 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 99.1797 % (> 98.9560 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested

reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20682     | 22463               | 12.31                        | 36.14                           |
| 20683     | 22463               | 4.03                         | 35.70                           |
| 20706     | 22463               | 12.67                        | 36.37                           |
| 20913     | 22463               | 5.72                         | 35.27                           |
| 21455     | 22463               | 12.26                        | 37.77                           |
| 21487     | 22463               | 4.66                         | 39.20                           |
| 22463     | 22463               | 0.00                         | 35.28                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Citrulline**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21095-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Citrulline; Citrullinum; L-citrulline

### Special notes

When selecting the *Citrulline* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Citrulline*:

| Supplier | Substance  | Batch      | Sample ID | Spectra | Certificate |
|----------|------------|------------|-----------|---------|-------------|
| Euro OTC | Citrulline | 1310015-01 | 21095     | 40      | 20131120    |
| Euro OTC | Citrulline | 1403021-01 | 21565     | 40      | 1411031     |
| Euro OTC | Citrulline | 1506014    | 21828     | 40      | 20150624*   |
| Euro OTC | Citrulline | 1604038    | 22560     | 40      | 20160523*   |
| Euro OTC | Citrulline | 1703036    | 23175     | 40      | 20170418*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Citrulline*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 159 spectra of 5 reference samples from the substance/substance group *Citrulline*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Euro OTC | Citrulline | 1403021-01       | 21565 <sup>†</sup> | 19      |
| Euro OTC | Citrulline | 1506014          | 21828 <sup>†</sup> | 20      |
| Euro OTC | Citrulline | 1609013          | 22866              | 40      |
| Euro OTC | Citrulline | 1707003          | 23538              | 40      |
| Fagron   | Citrulline | 16D11-B02-326797 | 23567              | 40      |

- 146 570 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 4 spectra from 3 *Apo-Ident* customers from 4 batches from the substance/substance group *Citrulline*.

| Supplier                | Substance  | Batch       | Spectra |
|-------------------------|------------|-------------|---------|
| Euro OTC                | Citrulline | 16040038-01 | 1       |
| Gall-Pharma GmbH/Noweda | Citrulline |             | 1       |
| Euro OTC                | Citrulline | L1506014-01 | 1       |
| Gall-Pharma GmbH        | Citrulline |             | 1       |

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Citrulline* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Citrulline* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 159           | 0              | 146 570       |
| <b>Type C</b> | 0              | 4             | 0              | 69 629        |

The substance/substance group *Citrulline* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.2264 %) |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21095     | 21565               | 9.76                         | 47.24                           |
| 21565     | 21565               | 0.00                         | 47.12                           |
| 21828     | 21828               | 0.00                         | 45.16                           |
| 22560     | 22560               | 0.00                         | 44.49                           |
| 23175     | 23175               | 0.00                         | 44.31                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Clindamycin hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20214-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Clindamycin hydrochloride; Clindamycini hydrochloridum; Clindamycinum hydrochloricum

### Special notes

When selecting the *Clindamycin hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Clindamycin hydrochloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Euro OTC | Clindamycin hydr... | 1111058-01 | 20757     | 80      | 20120516    |
| Fagron   | Clindamycin hydr... | 13G24-N09  | 21224     | 40      | 1412075     |
| Euro OTC | Clindamycin hydr... | 1511004    | 21996     | 40      | 20151123*   |
| Euro OTC | Clindamycin hydr... | 1510038    | 22224     | 40      | 20151120*   |
| Caelo    | Clindamycin hydr... | 15392809   | 22958     | 40      | 20151204    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 5 reference samples from the substance/substance group *Clindamycin hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 272 spectra of 8 reference samples from the substance/substance group *Clindamycin hydrochloride*.

| Supplier | Substance                 | Batch            | Sample ID          | Spectra |
|----------|---------------------------|------------------|--------------------|---------|
| Euro OTC | Clindamycin hydrochloride | 2908019-01       | 20214              | 40      |
| Euro OTC | Clindamycin hydrochloride | 1401041-01       | 21239              | 40      |
| Euro OTC | Clindamycin hydrochloride | 1511004          | 21996 <sup>†</sup> | 20      |
| Euro OTC | Clindamycin hydrochloride | 1510038          | 22224 <sup>†</sup> | 20      |
| Caelo    | Clindamycin hydrochloride | 15392817         | 23245              | 40      |
| Fagron   | Clindamycin hydrochloride | 16D05-B08-332106 | 23264              | 40      |
| Caelo    | Clindamycin hydrochloride | 153928           | 23365              | 32      |
| Caelo    | Clindamycin hydrochloride | 172093           | 23681              | 40      |

- 146 457 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 162 spectra from 70 *Apo-Ident* customers from 75 batches from the substance/substance group *Clindamycin hydrochloride*.

| Supplier          | Substance                 | Batch            | Spectra |
|-------------------|---------------------------|------------------|---------|
| Euro OTC          | Clindamycin hydrochloride | 4988149          | 1       |
| Euro OTC          | Clindamycin hydrochloride | 813M-03534       | 1       |
| Euro OTC          | Clindamycin hydrochloride | 1111058-01       | 7       |
| Euro OTC          | Clindamycin hydrochloride | 1111058-03       | 3       |
| Phönix            | Clindamycin hydrochloride | 12H30-N04        | 1       |
| Euro OTC          | Clindamycin hydrochloride | 130709X8         | 1       |
| Fagron            | Clindamycin hydrochloride | 13A22-N01        | 7       |
| Fagron            | Clindamycin hydrochloride | 13G24N09         | 1       |
| Fagron            | Clindamycin hydrochloride | 13G24-N09        | 11      |
| Caelo             | Clindamycin hydrochloride | 13G24-N09        | 1       |
| Fagron            | Clindamycin hydrochloride | 13J03-B02288654  | 1       |
| Fagron            | Clindamycin hydrochloride | 13J03-B02-288653 | 1       |
| Fagron            | Clindamycin hydrochloride | 13J03-B02        | 1       |
| Fagron            | Clindamycin hydrochloride | 13j03-B02-288653 | 1       |
| Fagron            | Clindamycin hydrochloride | 13J03B02288654   | 1       |
| Fagron            | Clindamycin hydrochloride | 13J03-B02-288654 | 4       |
| Fagron            | Clindamycin hydrochloride | 13J03-B02-288655 | 3       |
| Euro OTC          | Clindamycin hydrochloride | 1401041-01       | 11      |
| Caelo             | Clindamycin hydrochloride | 1401041-01       | 2       |
| EuRho             | Clindamycin hydrochloride | 1401041-01       | 1       |
| Euro OTC          | Clindamycin hydrochloride | 140104101        | 1       |
| Euro OTC          | Clindamycin hydrochloride | 1401041-02       | 3       |
| Euro OTC          | Clindamycin hydrochloride | 140104102        | 2       |
| EuRho             | Clindamycin hydrochloride | 1401041-02       | 1       |
| Fagron            | Clindamycin hydrochloride | 14D23-B03        | 1       |
| Fagron            | Clindamycin hydrochloride | 14K04-B05-304995 | 1       |
| Fagron            | Clindamycin hydrochloride | 14K04-B05-304996 | 1       |
| Caelo             | Clindamycin hydrochloride | 14K04B05309851   | 1       |
| Fagron            | Clindamycin hydrochloride | 14K04-B05-313090 | 1       |
| Euro OTC          | Clindamycin hydrochloride | 1510038-01       | 6       |
| Euro/Gehe16.03.16 | Clindamycin hydrochloride | 1510038-01       | 1       |
| Eurho/Noweda      | Clindamycin hydrochloride | 1510038-01       | 1       |
| Caelo             | Clindamycin hydrochloride | 151003801        | 1       |
| Euro OTC          | Clindamycin hydrochloride | 1511004-01       | 8       |
| Caelo             | Clindamycin hydrochloride | 1511004-01       | 1       |
| Sanacorp          | Clindamycin hydrochloride | 1511004-03       | 1       |
| Phönix            | Clindamycin hydrochloride | 15392803         | 1       |
| Caelo             | Clindamycin hydrochloride | 15392805         | 1       |
| Caelo             | Clindamycin hydrochloride | 15392815         | 1       |
| Fagron            | Clindamycin hydrochloride | 15E06-B12-311886 | 3       |
| Fagron            | Clindamycin hydrochloride | 15E06-B12-313089 | 2       |
| Fagron            | Clindamycin hydrochloride | 15E06-B12-314066 | 2       |
| Fagron            | Clindamycin hydrochloride | 15L22-B03-318786 | 1       |
| Fagron            | Clindamycin hydrochloride | 15L22-B03-318787 | 1       |
| Caelo             | Clindamycin hydrochloride | 15L22-B03-318788 | 1       |
| Fagron            | Clindamycin hydrochloride | 1600324C         | 1       |
| Fagron            | Clindamycin hydrochloride | 16D05-B08        | 2       |
| Fagron            | Clindamycin hydrochloride | 16D05-B08-321002 | 1       |
| Fagron            | Clindamycin hydrochloride | 16D05-B08-320327 | 1       |
| Fagron            | Clindamycin hydrochloride | 16D05-B08-321572 | 1       |
| Fagron            | Clindamycin hydrochloride | 16D05-B08-323321 | 1       |
| Fagron            | Clindamycin hydrochloride | 16D05-B08-325087 | 2       |

*continued on the next page*

continued from previous page

| Supplier           | Substance                 | Batch             | Spectra |
|--------------------|---------------------------|-------------------|---------|
| Cealo/AHD          | Clindamycin hydrochloride | 16D05-B08-325088  | 1       |
| Fagron             | Clindamycin hydrochloride | 16D05-B08-325088  | 1       |
| Fagron             | Clindamycin hydrochloride | 16D05-B08-327127  | 1       |
| Phoenix            | Clindamycin hydrochloride | 16D05-B08-327127  | 1       |
| Euro OTC           | Clindamycin hydrochloride | 16D05-B08-328259  | 1       |
| Euro OTC           | Clindamycin hydrochloride | 25071401          | 1       |
| Fagron             | Clindamycin hydrochloride | 2714Q-03534       | 1       |
| Euro OTC           | Clindamycin hydrochloride | 2908019V-03       | 4       |
| Euro OTC           | Clindamycin hydrochloride | 700168            | 1       |
| Fagron             | Clindamycin hydrochloride | P003WS13091401    | 1       |
| Euro OTC           | Clindamycin hydrochloride | T03-05/1401041-01 | 1       |
| Cealo              | Clindamycin hydrochloride |                   | 1       |
| Großhandel         | Clindamycin hydrochloride | 1111058-01        | 1       |
| Europharm/Otto     | Clindamycin hydrochloride | 1111058-01        | 1       |
| Cealo              | Clindamycin hydrochloride | 1111058-01        | 1       |
| Euro OTC           | Clindamycin hydrochloride | 1111058-02        | 3       |
| Cealo              | Clindamycin hydrochloride | 1111058-03        | 1       |
| Fagron             | Clindamycin hydrochloride | 11L20-No5         | 1       |
| Fagron             | Clindamycin hydrochloride | 14D23-B03-295477  | 2       |
| Phoenix 19.08.2010 | Clindamycin hydrochloride | 2908019-01phoen   | 1       |
| Noweda             | Clindamycin hydrochloride | 2908019V-03       | 1       |
| Euro OTC           | Clindamycin hydrochloride | 111158-01         | 1       |
| Gehe               | Clindamycin hydrochloride | 11K04-N12         | 1       |
| Gehe               | Clindamycin hydrochloride | 11E12-N02         | 1       |
| Cealo              | Clindamycin hydrochloride | 11K04-N12         | 1       |
| Fagron             | Clindamycin hydrochloride | 12C19-N06         | 1       |
| Fagron             | Clindamycin hydrochloride | 12F19-N07         | 3       |
| Fagron             | Clindamycin hydrochloride | 12H30-N04         | 1       |
| AHD                | Clindamycin hydrochloride | 130402X5          | 1       |
| Gehe               | Clindamycin hydrochloride | 13a22-n01         | 1       |
| Gehe               | Clindamycin hydrochloride | 13A22-N01         | 1       |
| Fagron             | Clindamycin hydrochloride | 13C15-N06         | 1       |
| Fagron             | Clindamycin hydrochloride | 13G24-N09         | 1       |
| Fagron             | Clindamycin hydrochloride | 14K04-B05-304997  | 1       |
| Fagron             | Clindamycin hydrochloride | 15E06B12-310472   | 1       |
| Cealo              | Clindamycin hydrochloride | 15L22-B03-316671  | 1       |
| Gehe               | Clindamycin hydrochloride | 700168-0002       | 1       |
| Fagron             | Clindamycin hydrochloride | 7BS64T1J0023      | 1       |
| Fagron             | Clindamycin hydrochloride | P003-WS10100301   | 1       |
| Cealo              | Clindamycin hydrochloride | P-003-WS10100301  | 1       |
| Fagron             | Clindamycin hydrochloride | 12C19N06          | 1       |

- 69 471 spectra from 414 *Apo-Ident* customers from a total of 23 728 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Clindamycin hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Clindamycin hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 240           | 0              | 71 146        |
| Type B | 0              | 247           | 25             | 146 457       |
| Type C | 0              | 148           | 14             | 69 471        |

The substance/substance group *Clindamycin hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 90.8088 % (> 89.7059 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 91.3580 % (> 89.5062 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20757     | 21996               | 3.23                         | 25.09                           |
| 21224     | 21224               | 0.00                         | 21.62                           |
| 21996     | 21996               | 0.00                         | 23.05                           |
| 22224     | 22224               | 0.00                         | 23.62                           |
| 22958     | 21224               | 2.70                         | 22.94                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | Clindamycin-2-dihydrogen phosphate                              |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 21063-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Clindamycin-2-dihydrogen phosphate; Clindamycini phosphas; Clindamycinum phosphoricum

### Special notes

When selecting the *Clindamycin-2-dihydrogen phosphate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Clindamycin-2-dihydrogen phosphate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate        |
|----------|---------------------|----------|-----------|---------|--------------------|
| Caelo    | Clindamycin-2-di... | 13166605 | 21063     | 40      | 1403485            |
| Caelo    | Clindamycin-2-di... | 13166605 | 21116     | 40      | 20130624           |
| Caelo    | Clindamycin-2-di... | 14257305 | 21798     | 40      | AR-15-FG-015412-01 |
| Caelo    | Clindamycin-2-di... | 15435801 | 22312     | 40      | AR-16-FG-009129-01 |
| Caelo    | Clindamycin-2-di... | 163265   | 23055     | 40      | 2061214*           |
| Caelo    | Clindamycin-2-di... | 16326504 | 23586     | 40      | AR-17-FG-022557-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Clindamycin-2-dihydrogen phosphate*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 5 reference samples from the substance/substance group *Clindamycin-2-dihydrogen phosphate*.

| Supplier | Substance                       | Batch    | Sample ID          | Spectra |
|----------|---------------------------------|----------|--------------------|---------|
| Caelo    | Clindamycin-2-dihydrogen pho... | 14257305 | 21798 <sup>†</sup> | 20      |
| Caelo    | Clindamycin-2-dihydrogen pho... | 15435801 | 22312 <sup>†</sup> | 20      |
| Caelo    | Clindamycin-2-dihydrogen pho... | 14257305 | 21798SI            | 60      |
| Caelo    | Clindamycin-2-dihydrogen pho... | 15435801 | 22312SI            | 60      |
| Caelo    | Clindamycin-2-dihydrogen pho... | 163265   | 23055SI            | 40      |

- 146 529 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Clindamycin-2-dihydrogen phosphate*.

| Supplier | Substance                       | Batch    | Spectra |
|----------|---------------------------------|----------|---------|
| Caelo    | Clindamycin-2-dihydrogen pho... | 14257305 | 1       |

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Clindamycin-2-dihydrogen phosphate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Clindamycin-2-dihydrogen phosphate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 124           | 76             | 146 529       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Clindamycin-2-dihydrogen phosphate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 62.0000 % (> 60.5000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21063     | 21063               | 0.00                         | 23.52                           |
| 21116     | 21063               | 5.48                         | 23.74                           |
| 21798     | 21798               | 0.00                         | 16.82                           |
| 22312     | 22312               | 0.00                         | 26.87                           |
| 23055     | 23055               | 0.00                         | 21.97                           |
| 23586     | 23586               | 0.00                         | 25.73                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Clioquinol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20095-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Clioquinol; Clioquinolum; Jodochloroxychinolinum

### Special notes

When selecting the *Clioquinol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Clioquinol*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate        |
|----------|------------|------------------|-----------|---------|--------------------|
| Caelo    | Clioquinol | 11304120         | 20895     | 40      | 20111208           |
| Fagron   | Clioquinol | 13I26-N15        | 21236     | 40      | 20131028           |
| Euro OTC | Clioquinol | 1309009-02       | 21246     | 40      | AR-15-FG-009542-01 |
| Fagron   | Clioquinol | 14I11-B03-300049 | 21913     | 40      | 20140926           |
| Euro OTC | Clioquinol | 1509038          | 21944     | 40      | 20151009*          |
| Fagron   | Clioquinol | 14I11-B03-300049 | 21972     | 40      | 20140926           |
| Caelo    | Clioquinol | 163072           | 23047     | 40      | 20161202*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 280 spectra of 7 reference samples from the substance/substance group *Clioquinol*. These samples are listed above in the [calibration samples](#) section.
- 71 106 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 210 spectra of 7 reference samples from the substance/substance group *Clioquinol*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Caelo    | Clioquinol | 13114413         | 21308              | 40      |
| Fagron   | Clioquinol | 14I11-B03-300049 | 21913 <sup>†</sup> | 20      |
| Euro OTC | Clioquinol | 1509038          | 21944 <sup>†</sup> | 20      |
| Fagron   | Clioquinol | 14I11-B03-300049 | 21972 <sup>†</sup> | 20      |
| Caelo    | Clioquinol | 16307206         | 22960              | 40      |
| Euro OTC | Clioquinol | 1612020          | 22985              | 40      |
| Caelo    | Clioquinol | 172046           | 23633              | 30      |

- 146 519 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 556 spectra from 229 *Apo-Ident* customers from 151 batches from the substance/substance group *Clioquinol*.

| Supplier                   | Substance  | Batch       | Spectra |
|----------------------------|------------|-------------|---------|
| Caelo                      | Clioquinol | 3041409     | 1       |
| Caelo                      | Clioquinol | 5031302     | 1       |
| Fagron                     | Clioquinol | 7D20-N03    | 1       |
| Fagron                     | Clioquinol | 1005090024  | 1       |
| Noweda                     | Clioquinol | 10057206    | 1       |
| Fagron                     | Clioquinol | 10341601    | 2       |
| Caelo                      | Clioquinol | 10341601    | 2       |
| Caelo                      | Clioquinol | 10341605    | 4       |
| Caelo                      | Clioquinol | 10341608    | 2       |
| Gehe                       | Clioquinol | 1102022-01  | 1       |
| Euro OTC                   | Clioquinol | 1102022-01  | 2       |
| Euro OTC                   | Clioquinol | 1102022-02  | 3       |
| Phönix                     | Clioquinol | 1102022-02  | 4       |
| Caelo                      | Clioquinol | 11304102    | 9       |
| Caelo                      | Clioquinol | 1130312     | 1       |
| Erika Apotheke             | Clioquinol | 11304102    | 1       |
| Caelo                      | Clioquinol | 11304103    | 2       |
| Caelo                      | Clioquinol | 11304105    | 5       |
| Caelo                      | Clioquinol | 11304107    | 6       |
| Noweda                     | Clioquinol | 11304107    | 1       |
| Caelo                      | Clioquinol | 11304109    | 3       |
| Caelo                      | Clioquinol | 11304111    | 3       |
| Sanacorp                   | Clioquinol | 11304111    | 1       |
| Noweda                     | Clioquinol | 11304111    | 1       |
| Caelo                      | Clioquinol | 11304112    | 7       |
| Noweda                     | Clioquinol | 11304112    | 1       |
| Fagron                     | Clioquinol | 11304112    | 1       |
| Caelo                      | Clioquinol | 11304113    | 4       |
| Caelo                      | Clioquinol | 11304116    | 4       |
| Caelo                      | Clioquinol | 11304117    | 12      |
| Caelo                      | Clioquinol | 11304119    | 3       |
| Caelo                      | Clioquinol | 11304120    | 15      |
| Phoenix                    | Clioquinol | 11304119    | 1       |
| Alliance Health 21.10.2... | Clioquinol | 11304120    | 1       |
| Fagron                     | Clioquinol | 11304120    | 1       |
| Caelo                      | Clioquinol | 11304124    | 12      |
| Phönix Gotha               | Clioquinol | 11304124    | 1       |
| Sanacorp                   | Clioquinol | 11304124    | 1       |
| Caelo                      | Clioquinol | 11B11-N19   | 1       |
| Fagron                     | Clioquinol | 11G20-N09   | 3       |
| Großhandel                 | Clioquinol | 11G20-N09   | 1       |
| Fagron                     | Clioquinol | 11K21-N18   | 4       |
| Fagron                     | Clioquinol | 11K21N18    | 1       |
| Noweda                     | Clioquinol | 120103401   | 1       |
| Caelo                      | Clioquinol | 1201034-01  | 1       |
| Euro OTC                   | Clioquinol | 1201034-01  | 8       |
| Anzag am 27.12.12          | Clioquinol | 1201034-01  | 1       |
| Euro OTC                   | Clioquinol | 1201034-02  | 9       |
| Noweda                     | Clioquinol | 1201034-02  | 2       |
| Phönix                     | Clioquinol | 1201034-02  | 1       |
| Gehe 09.04.2013            | Clioquinol | 1201034-02  | 2       |
| Caelo                      | Clioquinol | 1201034-02  | 2       |
| EuRho                      | Clioquinol | 1201034-02  | 1       |
| Fagron                     | Clioquinol | 1205110014  | 1       |
| Euro OTC                   | Clioquinol | 121034-02   | 1       |
| Euro OTC                   | Clioquinol | 1213A-02562 | 1       |

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| <b>Supplier</b>   | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|-------------------|------------------|------------------|----------------|
| Caelo             | Clioquinol       | 1214I02562       | 1              |
| Fagron            | Clioquinol       | 12D02-N11        | 1              |
| Fagron            | Clioquinol       | 12F20-N05        | 5              |
| Caelo             | Clioquinol       | 12F20-N05        | 1              |
| Fagron            | Clioquinol       | 12L04-N08        | 7              |
| Anzag             | Clioquinol       | 12L04-N08        | 1              |
| Großhandel        | Clioquinol       | 12L04-N08        | 1              |
| Caelo             | Clioquinol       | 12L04-N08        | 2              |
| Fargron           | Clioquinol       | 12L04-N08        | 1              |
| Fagron            | Clioquinol       | 13/26-N15        | 2              |
| Euro OTC          | Clioquinol       | 13010104-03      | 1              |
| Euro OTC          | Clioquinol       | 1301014-01       | 3              |
| Euro OTC          | Clioquinol       | 1301014-02       | 5              |
| Axyntis Group     | Clioquinol       | 1301014-02       | 1              |
| Euro OTC          | Clioquinol       | 1303009-02       | 1              |
| Axyntis Group     | Clioquinol       | 1301014-03       | 1              |
| Euro OTC          | Clioquinol       | 1301014-0Z       | 1              |
| Fagron            | Clioquinol       | 1305120028       | 1              |
| Euro OTC          | Clioquinol       | 1309009-01       | 6              |
| Cealo/Sanacorp    | Clioquinol       | 1309009-01       | 1              |
| Noweda            | Clioquinol       | 1309009-01       | 1              |
| Fagron            | Clioquinol       | 1309009-01       | 1              |
| EuRho             | Clioquinol       | 1309009-02       | 1              |
| Euro OTC          | Clioquinol       | 1309009-02       | 10             |
| Caelo             | Clioquinol       | 1309009-02       | 1              |
| Euro OTC          | Clioquinol       | 130900902        | 1              |
| Phönix            | Clioquinol       | 1309009-02       | 1              |
| Euro OTC          | Clioquinol       | 1309009-03       | 1              |
| Caelo             | Clioquinol       | 13114404         | 3              |
| Phoenix           | Clioquinol       | 13114408         | 2              |
| Caelo             | Clioquinol       | 13114406         | 1              |
| Caelo             | Clioquinol       | 13114408         | 4              |
| Caelo             | Clioquinol       | 13114410         | 3              |
| Caelo             | Clioquinol       | 13114413         | 10             |
| Synthexim/Phoenix | Clioquinol       | 13114415         | 1              |
| Caelo             | Clioquinol       | 13114415         | 3              |
| Caelo             | Clioquinol       | 13114417         | 7              |
| Fagron            | Clioquinol       | 13114417         | 1              |
| Phoenix           | Clioquinol       | 13114417         | 1              |
| Phönix            | Clioquinol       | 13114417         | 1              |
| Caelo             | Clioquinol       | 13114418         | 7              |
| GEHE 04.08.2014   | Clioquinol       | 13114418         | 1              |
| Noweda 30.09.2014 | Clioquinol       | 13114422         | 1              |
| Caelo             | Clioquinol       | 13114422         | 8              |
| Sanacorp          | Clioquinol       | 13114422         | 1              |
| Caelo             | Clioquinol       | 13114423         | 12             |
| Caelo             | Clioquinol       | 13114424         | 13             |
| Fagron            | Clioquinol       | 13114424         | 1              |
| Caelo             | Clioquinol       | 13114427         | 3              |
| Fagron            | Clioquinol       | 1326-N15         | 3              |
| Caelo             | Clioquinol       | 13A29-N07        | 1              |
| Fagron            | Clioquinol       | 13A29-N07        | 6              |
| Großhandel        | Clioquinol       | 13D15-N01        | 2              |
| Fagron            | Clioquinol       | 13D15-N01        | 6              |
| Fagron            | Clioquinol       | 13DS15-N01       | 1              |
| Caelo             | Clioquinol       | 13F12-N20        | 1              |
| Großhandel        | Clioquinol       | 13F12-N20        | 1              |
| Fagron            | Clioquinol       | 13F12-N20        | 2              |
| Fagron            | Clioquinol       | 13F12-N200463480 | 1              |
| Fagron            | Clioquinol       | 13I26-N15        | 6              |

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| Supplier                 | Substance  | Batch             | Spectra |
|--------------------------|------------|-------------------|---------|
| Fagron                   | Clioquinol | 13I26N15          | 1       |
| Caelo                    | Clioquinol | 13I26-N15         | 1       |
| Nachprüfung              | Clioquinol | 13L26-N15         | 2       |
| Unisan                   | Clioquinol | 14/11-B03         | 1       |
| Fagron                   | Clioquinol | 14/11-B03-300049  | 5       |
| Fagron                   | Clioquinol |                   | 1       |
| Caelo                    | Clioquinol | 14/11-B03-309181  | 1       |
| Fagron                   | Clioquinol | 14/11-B03-309048  | 1       |
| Caelo                    | Clioquinol | 14/11-BG03-309181 | 1       |
| Caelo                    | Clioquinol | 14/-B03-309181    | 1       |
| Caelo                    | Clioquinol | 1405080036        | 1       |
| Caelo                    | Clioquinol | 1405080031        | 1       |
| Fagron                   | Clioquinol | 14052014C         | 1       |
| Euro OTC                 | Clioquinol | 14090131-02       | 1       |
| Euro OTC                 | Clioquinol | 1409031-01        | 8       |
| Euro OTC                 | Clioquinol | 140903101         | 1       |
| Euro OTC                 | Clioquinol | 1409031-02        | 8       |
| Fagron                   | Clioquinol | 1411-B03-300049   | 1       |
| Caelo                    | Clioquinol | 14353120          | 1       |
| Caelo                    | Clioquinol | 14359102          | 7       |
| Noweda                   | Clioquinol | 14359103          | 1       |
| Caelo                    | Clioquinol | 14359103          | 10      |
| Cael Sanacorp 05.02.2016 | Clioquinol | 14359103          | 1       |
| Caelo                    | Clioquinol | 14359107          | 1       |
| Caelo                    | Clioquinol | 14359111          | 12      |
| caesar&loretz,Phönix     | Clioquinol | 14359111          | 1       |
| Caelo                    | Clioquinol | 14359112          | 15      |
| Caelo                    | Clioquinol | 14359113          | 1       |
| Caelo                    | Clioquinol | 14359117          | 4       |
| Caelo                    | Clioquinol | 14359118          | 2       |
| Bombastus                | Clioquinol | 14359118          | 1       |
| Fagron                   | Clioquinol | 14359118          | 1       |
| Caelo                    | Clioquinol | 14359119          | 2       |
| Caelo                    | Clioquinol | 14359120          | 9       |
| Noweda                   | Clioquinol | 14359120          | 1       |
| Caelo                    | Clioquinol | 14359123          | 1       |
| wepa/Sanaco              | Clioquinol | 1439118           | 1       |
| Fagron                   | Clioquinol | 14C21806293104    | 1       |
| Phönix                   | Clioquinol | 14C21-B06         | 1       |
| Fagron                   | Clioquinol | 14C21-B06         | 2       |
| Fagron                   | Clioquinol | 14C21-B06-293104  | 3       |
| Fagron                   | Clioquinol | 14c21B06293104    | 1       |
| Caelo                    | Clioquinol | 14C21-B06-293104  | 1       |
| Fagron                   | Clioquinol | 14-C21-B06-293132 | 1       |
| Fagron                   | Clioquinol | 14C21-B06-293132  | 2       |
| Fagron                   | Clioquinol | 14C21-B06-297159  | 3       |
| Phönix                   | Clioquinol | 14C21-B08         | 1       |
| Fagron                   | Clioquinol | 14C21-B08         | 1       |
| Fagron                   | Clioquinol | 14I11-B03         | 2       |
| Fagron                   | Clioquinol | 14I11-B03-300049  | 3       |
| Fagron                   | Clioquinol | 14I11-B03-3000049 | 1       |
| Fagron                   | Clioquinol | 14I11-B03-309181  | 2       |
| Euro OTC                 | Clioquinol | 1509038           | 1       |
| Euro OTC                 | Clioquinol | 1509038-01        | 10      |
| Euro OTC                 | Clioquinol | 150903801         | 1       |
| Caelo                    | Clioquinol | 1509038-01        | 1       |
| Euro OTC                 | Clioquinol | 1509038-02        | 11      |
| Euro OTC                 | Clioquinol | 150903802         | 1       |
| Apo-ident                | Clioquinol | 1509038-02        | 1       |
| EURO / Sanacorp          | Clioquinol | 150903802         | 1       |

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| Supplier    | Substance  | Batch                | Spectra |
|-------------|------------|----------------------|---------|
| Euro OTC    | Clioquinol | 1509038-03           | 5       |
| Gehe        | Clioquinol | 1509038-03           | 1       |
| Fagron      | Clioquinol | 15L30-321899         | 1       |
| Euro OTC    | Clioquinol | 1509038-31           | 1       |
| Fagron      | Clioquinol | 15L30-B05-314974     | 3       |
| Fagron      | Clioquinol | 15L30-B05-319616     | 1       |
| Fagron      | Clioquinol | 15L30-B05-321899     | 1       |
| Caelo       | Clioquinol | 16021505             | 1       |
| Caelo       | Clioquinol | 16307203             | 1       |
| Caelo       | Clioquinol | 16307205             | 5       |
| Caelo       | Clioquinol | 16307206             | 7       |
| Caelo       | Clioquinol | 16307207             | 5       |
| Fagron      | Clioquinol | 16J18-B04-329141     | 2       |
| Euro OTC    | Clioquinol | 2507212562           | 1       |
| Fagron      | Clioquinol | 2014Q2562            | 1       |
| Fagron      | Clioquinol | 2514U2562            | 1       |
| Fagron      | Clioquinol | 28031401             | 1       |
| Caelo       | Clioquinol | 2814M-02562          | 1       |
| Nachprüfung | Clioquinol | 3021U-02562          | 1       |
| Caelo       | Clioquinol | 3513I-02562          | 1       |
| Caelo       | Clioquinol | 3713A2562            | 1       |
| Fagron      | Clioquinol | 3916U-02562          | 1       |
| Caelo       | Clioquinol | 4214Q-02562          | 1       |
| Caelo       | Clioquinol | 5089                 | 1       |
| Caelo       | Clioquinol | 4613E2562            | 1       |
| Caelo       | Clioquinol | 5213A2562            | 1       |
| Caelo       | Clioquinol |                      | 1       |
| Sanacorp    | Clioquinol | 8/AKD4               | 1       |
| Euro OTC    | Clioquinol |                      | 1       |
| Caelo       | Clioquinol | 10341510             | 1       |
| Euro OTC    | Clioquinol | 1305070109           | 1       |
| Caelo       | Clioquinol | 130900903            | 1       |
| Chiesi/Gehe | Clioquinol | 13114421             | 1       |
| Caelo       | Clioquinol | 130114-02            | 1       |
| Sanacorp    | Clioquinol | 1201034-01           | 1       |
| Fagron      | Clioquinol | 13A29-N07-3398310111 | 1       |
| VDL         | Clioquinol | 131144131            | 1       |

- 69 077 spectra from 414 *Apo-Ident* customers from a total of 23 652 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Clioquinol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Clioquinol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 280           | 0              | 71 106        |
| Type B | 0              | 210           | 0              | 146 519       |
| Type C | 0              | 477           | 79             | 69 077        |

The substance/substance group *Clioquinol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.8571 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.1429 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 85.7914 % (> 85.2518 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 20895            | 23047                      | 7.33                                | 86.67                                  |
| 21236            | 21246                      | 2.79                                | 70.18                                  |
| 21246            | 21246                      | 0.00                                | 73.03                                  |
| 21913            | 21944                      | 3.60                                | 83.08                                  |
| 21944            | 21944                      | 0.00                                | 73.01                                  |
| 21972            | 21944                      | 4.00                                | 79.67                                  |
| 23047            | 23047                      | 0.00                                | 78.94                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Clobetasol propionate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20030-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Clobetasol propionate; Clobetasoli propionas; Clobetasolum propionicum

### Special notes

When selecting the *Clobetasol propionate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Clobetasol propionate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------|-----------|---------|--------------------|
| Caelo    | Clobetasol propi... | 13134705   | 21092     | 80      | AR-15-FG-005328-01 |
| Caelo    | Clobetasol propi... | 13269505   | 21473     | 40      | AR-15-FG-000622-02 |
| Euro OTC | Clobetasol propi... | 1211021-04 | 21611     | 40      | 1605044            |
| Caelo    | Clobetasol propi... | 14338001   | 21802     | 40      | AR-16-FG-008581-01 |
| Caelo    | Clobetasol propi... | 14338001   | 21896     | 40      | 1607072            |

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| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate        |
|----------|---------------------|----------|-----------|---------|--------------------|
| Euro OTC | Clobetasol propi... | 1606022  | 22714     | 40      | 20160713*          |
| Caelo    | Clobetasol propi... | 15439504 | 22724     | 40      | 20160204           |
| Caelo    | Clobetasol propi... | 14338001 | 21802SI   | 39      | AR-16-FG-008581-01 |
| Caelo    | Clobetasol propi... | 14338001 | 21896SI   | 30      | 1607072            |
| Euro OTC | Clobetasol propi... | 1606022  | 22714SI   | 40      | 20160713*          |
| Caelo    | Clobetasol propi... | 15439504 | 22724SI   | 37      | 20160204           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 466 spectra of 11 reference samples from the substance/substance group *Clobetasol propionate*. These samples are listed above in the [calibration samples](#) section.
- 70 920 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 506 spectra of 15 reference samples from the substance/substance group *Clobetasol propionate*.

| Supplier    | Substance             | Batch      | Sample ID            | Spectra |
|-------------|-----------------------|------------|----------------------|---------|
| Caelo       | Clobetasol propionate | 82805079   | 20030                | 100     |
| Euro OTC    | Clobetasol propionate | pending    | 21013                | 54      |
| zu erfassen | Clobetasol propionate | pending    | 21017                | 20      |
| Caelo       | Clobetasol propionate | 13269505   | 21473 <sup>†</sup>   | 20      |
| Euro OTC    | Clobetasol propionate | 1211021-04 | 21611 <sup>†</sup>   | 20      |
| Caelo       | Clobetasol propionate | 14338001   | 21802 <sup>†</sup>   | 20      |
| Caelo       | Clobetasol propionate | 14338001   | 21896 <sup>†</sup>   | 19      |
| Caelo       | Clobetasol propionate | 161067     | 22470                | 60      |
| Euro OTC    | Clobetasol propionate | 1704020    | 23397                | 40      |
| Caelo       | Clobetasol propionate | 170967     | 23665                | 30      |
| Caelo       | Clobetasol propionate | 14338001   | 21802SI <sup>†</sup> | 20      |
| Caelo       | Clobetasol propionate | 14338001   | 21896SI <sup>†</sup> | 15      |
| Caelo       | Clobetasol propionate | 161067     | 22470SI              | 48      |
| Euro OTC    | Clobetasol propionate | 1704020    | 23397SI              | 20      |
| Caelo       | Clobetasol propionate | 170967     | 23665SI              | 20      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

- 146 223 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 957 spectra from 295 *Apo-Ident* customers from 234 batches from the substance/substance group *Clobetasol propionate*.

| Supplier                | Substance             | Batch      | Spectra |
|-------------------------|-----------------------|------------|---------|
| Gehe                    | Clobetasol propionate | 12342310   | 2       |
| Euro OTC                | Clobetasol propionate | 1072015D   | 1       |
| Euro OTC                | Clobetasol propionate | 4091512    | 1       |
| Symbiotica Spec./Phönix | Clobetasol propionate | 1108044-04 | 1       |
| Caelo                   | Clobetasol propionate | 11300707   | 4       |
| Fagron                  | Clobetasol propionate | 11C16-N01  | 1       |
| Fagron                  | Clobetasol propionate | 11129-N07  | 1       |
| Euro OTC                | Clobetasol propionate | 1211021/02 | 1       |
| Fagron                  | Clobetasol propionate | 1211021    | 1       |
| Euro OTC                | Clobetasol propionate | 1211021-02 | 33      |
| GEHE 21.03.2014         | Clobetasol propionate | 1211021-02 | 1       |
| Phönix Gotha            | Clobetasol propionate | 1211021-02 | 3       |
| Fagron                  | Clobetasol propionate | 1211021-03 | 2       |
| Euro OTC                | Clobetasol propionate | 1211021-03 | 24      |
| Phoenix 02.04.2014      | Clobetasol propionate | 1211021-03 | 3       |
| Apomix/Phönix           | Clobetasol propionate | 1211021-03 | 1       |
| Euro OTC                | Clobetasol propionate | 1211021-04 | 20      |
| Caelo                   | Clobetasol propionate | 121102104  | 1       |
| Euro OTC                | Clobetasol propionate | 121121-04  | 1       |
| Caelo                   | Clobetasol propionate | 12342309   | 16      |
| Caelo                   | Clobetasol propionate | 123645     | 1       |
| Fagron                  | Clobetasol propionate | 12E08-N04  | 14      |
| Euro OTC                | Clobetasol propionate | 13042015A  | 1       |
| Caelo                   | Clobetasol propionate | 13134701   | 16      |
| Noweda                  | Clobetasol propionate | 13134701   | 1       |
| Caelo                   | Clobetasol propionate | 13134704   | 4       |
| Caelo                   | Clobetasol propionate | 13134705   | 6       |
| Noweda                  | Clobetasol propionate | 13134705   | 1       |
| Fagron                  | Clobetasol propionate | 1314705    | 1       |
| Caelo                   | Clobetasol propionate | 13269501   | 3       |
| Caelo                   | Clobetasol propionate | 13269502   | 4       |
| Chiesi/ Now             | Clobetasol propionate | 13269503   | 3       |
| Noweda/Anzag            | Clobetasol propionate | 13269504   | 3       |
| Caelo                   | Clobetasol propionate | 13269504   | 7       |
| Caelo                   | Clobetasol propionate | 13269505   | 1       |
| Caelo                   | Clobetasol propionate | 13269507   | 2       |
| Sanacorp                | Clobetasol propionate | 13269507   | 1       |
| Caelo                   | Clobetasol propionate | 13269508   | 13      |
| sanacorp                | Clobetasol propionate | 13269508   | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier                   | Substance             | Batch            | Spectra |
|----------------------------|-----------------------|------------------|---------|
| Phönix Caesar u. Loretz    | Clobetasol propionate | 13269508         | 1       |
| Caelo                      | Clobetasol propionate | 13269510         | 2       |
| Caelo                      | Clobetasol propionate | 13269509         | 1       |
| Caelo                      | Clobetasol propionate | 1369504          | 1       |
| Fagron                     | Clobetasol propionate | 13A02-N04        | 15      |
| Fagron                     | Clobetasol propionate | 13G23-N01        | 22      |
| Caelo                      | Clobetasol propionate | 13G23-N01        | 3       |
| Sanacorp                   | Clobetasol propionate | 13g23n01         | 1       |
| Fagron                     | Clobetasol propionate | 13K08-B03-287728 | 1       |
| Fagron                     | Clobetasol propionate | 13K08-B30        | 2       |
| Caelo                      | Clobetasol propionate | 13K08-B30-287726 | 1       |
| Fagron                     | Clobetasol propionate | 13K08-B30-287726 | 2       |
| Raben-Apotheke Mildenau    | Clobetasol propionate | 13k08-b30-287727 | 1       |
| Fagron                     | Clobetasol propionate | 13K08-B30-287727 | 2       |
| Caelo                      | Clobetasol propionate | 13K08-B30-287728 | 1       |
| Phoenix                    | Clobetasol propionate | 13K08B30287728   | 1       |
| Fagron                     | Clobetasol propionate | 13K08-B30-287728 | 4       |
| Fagron                     | Clobetasol propionate | 13k08b30287728   | 1       |
| Caelo                      | Clobetasol propionate | 13k08b30287730   | 1       |
| Fagron                     | Clobetasol propionate | 13K08-B30-287729 | 2       |
| Fagron                     | Clobetasol propionate | 13K08-B30-287730 | 3       |
| Fagron                     | Clobetasol propionate | 13K08B30287730   | 1       |
| Euro OTC                   | Clobetasol propionate | 1408018-03       | 15      |
| Euro OTC                   | Clobetasol propionate | 1406018-01       | 1       |
| Euro OTC                   | Clobetasol propionate | 1408015-01       | 1       |
| Euro OTC                   | Clobetasol propionate | 1408018-01       | 15      |
| EuRho                      | Clobetasol propionate | 1408018-01       | 1       |
| Allianz Healthcare 02.0... | Clobetasol propionate | 1408018-01       | 1       |
| Noweda 19.05.2015          | Clobetasol propionate | 1408018-01       | 1       |
| Euro OTC                   | Clobetasol propionate | 140801801        | 1       |
| Noweda                     | Clobetasol propionate | 1408018-01       | 1       |
| Euro OTC                   | Clobetasol propionate | 1408018-02       | 45      |
| Caelo                      | Clobetasol propionate | 1408018-02       | 8       |
| Caelo                      | Clobetasol propionate | 1408018-03       | 5       |
| Symbiotica/Sanacorp        | Clobetasol propionate | 1408018-03       | 1       |
| Euro OTC                   | Clobetasol propionate | 140808-02        | 1       |
| Euro OT                    | Clobetasol propionate | 14081018-02      | 1       |
| Caelo                      | Clobetasol propionate | 14188501         | 5       |
| Caelo                      | Clobetasol propionate | 14188502         | 7       |
| Caelo                      | Clobetasol propionate | 14188503         | 14      |
| Caelo                      | Clobetasol propionate | 14188504         | 7       |
| Gehe                       | Clobetasol propionate | 14188504         | 1       |
| Caelo                      | Clobetasol propionate | 14188506         | 2       |
| Fischar                    | Clobetasol propionate | 14188506         | 1       |
| sanacorp                   | Clobetasol propionate | 14188506         | 1       |
| Caelo                      | Clobetasol propionate | 14338001         | 8       |
| Caelo                      | Clobetasol propionate | 14338002         | 1       |
| Caelo                      | Clobetasol propionate | 14338005         | 2       |
| Caelo                      | Clobetasol propionate | 14338006         | 9       |
| Farmabios S.p.A./Caesar... | Clobetasol propionate | 14338006         | 1       |
| Caelo                      | Clobetasol propionate | 14338007         | 5       |
| Noweda                     | Clobetasol propionate | 14338007         | 1       |
| Caelo                      | Clobetasol propionate | 14338008         | 4       |
| Caelo                      | Clobetasol propionate | 1438007          | 1       |
| Fagron                     | Clobetasol propionate | 14C03-B07        | 6       |
| Fargon                     | Clobetasol propionate | 14C03-B07        | 1       |
| Fagron                     | Clobetasol propionate | 14C03-B07-203562 | 1       |
| Fagron                     | Clobetasol propionate | 14C03-B07-293560 | 2       |
| Fagron                     | Clobetasol propionate | 14C03-B07-293561 | 2       |
| Fagron                     | Clobetasol propionate | 14C03-B07-293562 | 7       |

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| Supplier                    | Substance             | Batch            | Spectra |
|-----------------------------|-----------------------|------------------|---------|
| Sanacorp;19.03.15;87,60EUR  | Clobetasol propionate | 14C03-B07-293563 | 1       |
| Fagron                      | Clobetasol propionate | 14C03-B07-293563 | 1       |
| Fagron                      | Clobetasol propionate | 14C03-B07-305987 | 2       |
| Fagron                      | Clobetasol propionate | 14C03-B07-305986 | 1       |
| Fagron                      | Clobetasol propionate | 14G30B07302112   | 1       |
| Fagron                      | Clobetasol propionate | 14G30-B07-302112 | 1       |
| Caelo                       | Clobetasol propionate | 14G30B07302114   | 1       |
| Fagron                      | Clobetasol propionate | 14G30-B07-302113 | 2       |
| Fagron                      | Clobetasol propionate | 14G30-B07-302114 | 5       |
| Caelo                       | Clobetasol propionate | 14G30-B07-302114 | 1       |
| Fagron                      | Clobetasol propionate | 14G30-B07-302115 | 2       |
| Fagron                      | Clobetasol propionate | 14G30-B07-302116 | 4       |
| Fagron                      | Clobetasol propionate | 14G30-B07-303114 | 1       |
| Fagron                      | Clobetasol propionate | 15/15-B04-317698 | 1       |
| Caelo                       | Clobetasol propionate | 152340004        | 1       |
| Caelo                       | Clobetasol propionate | 15234001         | 2       |
| Caelo                       | Clobetasol propionate | 15234002         | 2       |
| Alliance H.                 | Clobetasol propionate | 15234002         | 2       |
| Caesar&Loretz GmbH          | Clobetasol propionate | 15234001         | 1       |
| Caelo                       | Clobetasol propionate | 15234003         | 9       |
| Euro OTC                    | Clobetasol propionate | 15234003         | 1       |
| Caelo                       | Clobetasol propionate | 15234004         | 17      |
| Noweda                      | Clobetasol propionate | 15234004         | 1       |
| Caelo                       | Clobetasol propionate | 15234009         | 2       |
| Caelo                       | Clobetasol propionate | 1524003          | 1       |
| Caelo                       | Clobetasol propionate | 15246001         | 4       |
| Caelo                       | Clobetasol propionate | 154390504        | 1       |
| Caelo                       | Clobetasol propionate | 15439501         | 2       |
| Caesar&Loretz GmbH          | Clobetasol propionate | 15439501         | 1       |
| Euro OTC                    | Clobetasol propionate | 15439501         | 1       |
| Caelo                       | Clobetasol propionate | 15439502         | 2       |
| Phoenix                     | Clobetasol propionate | 15439502         | 1       |
| Caelo                       | Clobetasol propionate | 15439503         | 13      |
| Caecolo/Noweda              | Clobetasol propionate | 15439503         | 1       |
| Caelo                       | Clobetasol propionate | 15439504         | 9       |
| 20.12.2016 Phoenix 17,49EUR | Clobetasol propionate | 15439504         | 1       |
| Caelo                       | Clobetasol propionate | 15439507         | 1       |
| Fagron                      | Clobetasol propionate | 15A14-B02-303125 | 8       |
| Caelo                       | Clobetasol propionate | 15A14-B02        | 1       |
| Fagro/Noweda                | Clobetasol propionate | 15A14-B02-303125 | 1       |
| Fagron                      | Clobetasol propionate | 15a14-b02-303125 | 1       |
| Fagron                      | Clobetasol propionate | 15C23-B02-310473 | 7       |
| Fagron                      | Clobetasol propionate | 15c23-b02-310473 | 2       |
| Fagron                      | Clobetasol propionate | 15C23-B02-310522 | 2       |
| Fagron                      | Clobetasol propionate | 15G01-B02-311578 | 2       |
| Fagron                      | Clobetasol propionate | 15H26-B03-312860 | 1       |
| Fagron                      | Clobetasol propionate | 15J15-B04-316615 | 1       |
| Fagron                      | Clobetasol propionate | 15J15-B04-317698 | 2       |
| Fagron                      | Clobetasol propionate | 15j15-B04-317698 | 1       |
| Caelo                       | Clobetasol propionate | 15J15-B04-317699 | 1       |
| Euro OTC                    | Clobetasol propionate | 16042014C        | 1       |
| Euro OTC                    | Clobetasol propionate | 1606022          | 1       |
| Euro OTC                    | Clobetasol propionate | 1606022-01       | 10      |
| Caelo                       | Clobetasol propionate | 160602201        | 1       |
| Symbiotitica/Noweda         | Clobetasol propionate | 1606022-01       | 1       |
| Noweda 6.4.17               | Clobetasol propionate | 1606022-01       | 1       |
| Euro OTC                    | Clobetasol propionate | 1606022-02       | 6       |
| Sanacorp                    | Clobetasol propionate | 1606022-02       | 1       |
| EuRho/Phoenix               | Clobetasol propionate | 160602202        | 1       |
| Gehe                        | Clobetasol propionate | 16106701         | 1       |

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| Supplier            | Substance             | Batch             | Spectra |
|---------------------|-----------------------|-------------------|---------|
| Caelo               | Clobetasol propionate | 16106702          | 3       |
| Caelo               | Clobetasol propionate | 16106703          | 6       |
| Caelo               | Clobetasol propionate | 16106704          | 2       |
| Gehe                | Clobetasol propionate | 16106704          | 1       |
| Caelo               | Clobetasol propionate | 16106709          | 2       |
| Caelo               | Clobetasol propionate | 16106710          | 4       |
| Caelo               | Clobetasol propionate | 16106711          | 2       |
| Caelo               | Clobetasol propionate | 16106713          | 2       |
| Caelo               | Clobetasol propionate | 16106715          | 1       |
| Caelo               | Clobetasol propionate | 16107704          | 1       |
| Caelo               | Clobetasol propionate | 1616703           | 1       |
| Caelo               | Clobetasol propionate | 16e04b12321033    | 1       |
| Fagron              | Clobetasol propionate | 16E04-B12         | 1       |
| Fagron              | Clobetasol propionate | 16E04-B12-321034  | 1       |
| Fagron              | Clobetasol propionate | 16E04-B12-321036  | 1       |
| Caelo               | Clobetasol propionate | 16E04-B12-321036  | 1       |
| Fagron              | Clobetasol propionate | 16E04-B12-322020  | 2       |
| Fagron              | Clobetasol propionate | 16G18-B02-325571  | 1       |
| Fagron              | Clobetasol propionate | 16G18-B02-32571   | 1       |
| Fagron              | Clobetasol propionate | 16H22-B07-328012  | 5       |
| Euro OTC            | Clobetasol propionate | 1704020-01        | 1       |
| Euro OTC            | Clobetasol propionate | 18111403          | 1       |
| Caelo               | Clobetasol propionate | 2014E-02835       | 1       |
| Caelo               | Clobetasol propionate | 2185              | 1       |
| Euro OTC            | Clobetasol propionate | 30092014A         | 1       |
| Caelo               | Clobetasol propionate | 39/AKD8           | 1       |
| Sanacorp            | Clobetasol propionate | 40/AKD12          | 1       |
| Euro OTC            | Clobetasol propionate | 4113Q-02835       | 1       |
| Audor Pharma        | Clobetasol propionate | APAPL/035/E-12C   | 2       |
| Audor Pharma        | Clobetasol propionate | APL/035/E-12C     | 1       |
| Audor Pharma        | Clobetasol propionate | APB0054/112010C   | 1       |
| Audor Pharma        | Clobetasol propionate | APL035E12C        | 1       |
| Oberlinden Apotheke | Clobetasol propionate | B0054/116010Mg60g | 1       |
| Caelo               | Clobetasol propionate | ap1/294/b-14      | 1       |
| Fagron              | Clobetasol propionate | NT0421M           | 5       |
|                     | Clobetasol propionate | 11/29-N07         | 1       |
| Euro OTC            | Clobetasol propionate | 1105044-04        | 1       |
| Euro OTC            | Clobetasol propionate | 1108044-02        | 12      |
| Euro OTC            | Clobetasol propionate | 1108044-03        | 19      |
| Caelo               | Clobetasol propionate | 1108044-03        | 2       |
| Euro OTC            | Clobetasol propionate | 1108044-037-16    | 1       |
| Euro OTC            | Clobetasol propionate | 1108044-04        | 18      |
| euroho/gehe         | Clobetasol propionate | 110804404         | 1       |
| Euro OTC            | Clobetasol propionate | 110804404         | 2       |
| Caelo               | Clobetasol propionate | 11300702          | 4       |
| Noweda              | Clobetasol propionate | 11300702          | 2       |
| Caelo               | Clobetasol propionate | 11300703          | 5       |
| Fagron              | Clobetasol propionate | 11h10-n02         | 2       |
| Fagron              | Clobetasol propionate | 11L12-N05         | 3       |
| Caelo               | Clobetasol propionate | 12107601          | 4       |
| Caelo               | Clobetasol propionate | 12107602          | 3       |
| Kehr                | Clobetasol propionate | 12107603          | 1       |
| Caelo               | Clobetasol propionate | 12107604          | 2       |
| Gehe                | Clobetasol propionate | 12107606          | 2       |
| Caelo               | Clobetasol propionate | 12107606          | 1       |
| Caelo               | Clobetasol propionate | 12107607          | 9       |
| Sanacorp            | Clobetasol propionate | 12107608          | 1       |
| Caelo               | Clobetasol propionate | 12107608          | 2       |
| Caelo               | Clobetasol propionate | 12107609          | 7       |
| Euro OTC            | Clobetasol propionate | 1211021-01        | 21      |

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| <b>Supplier</b>     | <b>Substance</b>      | <b>Batch</b>    | <b>Spectra</b> |
|---------------------|-----------------------|-----------------|----------------|
| Euro OTC            | Clobetasol propionate | 121102-01       | 1              |
| Euro OTC            | Clobetasol propionate | 121102101       | 2              |
| Phönix              | Clobetasol propionate | 1211021-01      | 1              |
| Caelo               | Clobetasol propionate | 1211021-04      | 1              |
| Euro OTC            | Clobetasol propionate | 121K021-01      | 1              |
| Caelo               | Clobetasol propionate | 12342303        | 2              |
| Caelo               | Clobetasol propionate | 12342306        | 9              |
| Caelo               | Clobetasol propionate | 12342308        | 1              |
| Caelo               | Clobetasol propionate | 12342310        | 7              |
| Fagron              | Clobetasol propionate | 12A02-N04       | 1              |
| Noweda              | Clobetasol propionate | 12E08-N04       | 2              |
| Fagron              | Clobetasol propionate | 12e08-n04       | 1              |
| Fagron              | Clobetasol propionate | 12E08N04        | 2              |
| Alliance Healthcare | Clobetasol propionate | 12J25-N01       | 1              |
| Fagron              | Clobetasol propionate | 12J25-N01       | 5              |
| Fagron              | Clobetasol propionate | 13134701        | 1              |
| Caelo               | Clobetasol propionate | 13134702        | 8              |
| Fagron              | Clobetasol propionate | 13A-N04         | 2              |
| Caelo               | Clobetasol propionate | 20121012-4      | 1              |
| Euro OTC            | Clobetasol propionate | 2111I-02835     | 1              |
| Caelo               | Clobetasol propionate | 23111202        | 1              |
| Caelo               | Clobetasol propionate | 3012Q02835      | 1              |
| Euro OTC            | Clobetasol propionate | CL0-BL2322/1012 | 3              |
| Fagron              | Clobetasol propionate | NS0486M         | 2              |
| Audor Pharma        | Clobetasol propionate | sieheBemerkung  | 1              |
| Caelo               | Clobetasol propionate | 11101315        | 2              |
| Anzag               | Clobetasol propionate | 12E08-N04       | 1              |
| Phönix              | Clobetasol propionate | 13134701        | 1              |
| Caelo               | Clobetasol propionate | 5071301         | 1              |
| GEHE                | Clobetasol propionate | 21022141/1      | 1              |
| Euro OTC            | Clobetasol propionate | 80616-1         | 1              |
| Phönix              | Clobetasol propionate |                 | 1              |
| Euro OTC            | Clobetasol propionate | 1004036-03      | 1              |
| Caelo               | Clobetasol propionate | 1004212835      | 1              |
| Gehe                | Clobetasol propionate | 10D21-N04       | 1              |
| Fagron              | Clobetasol propionate | 11/29-N07       | 1              |
| Fagron              | Clobetasol propionate | 11-05-N06       | 1              |
| Euro OTC            | Clobetasol propionate | 1108044         | 1              |
| Euro OTC            | Clobetasol propionate | 1108044-01      | 4              |
| Caelo               | Clobetasol propionate | 1108044-01      | 2              |
| Phönix Gotha        | Clobetasol propionate | 1108044-02      | 1              |
| Caelo               | Clobetasol propionate | 1108044-02      | 1              |
| Phönix, 30.10.2012  | Clobetasol propionate | 1108044-03      | 2              |
| Sanacorp            | Clobetasol propionate | 1108044-03      | 1              |
| Anzag 07.03.13      | Clobetasol propionate | 1108044-04      | 3              |
| Caelo               | Clobetasol propionate | 1108044-04      | 1              |
| Phönix Gotha        | Clobetasol propionate | 1108044-04      | 2              |
| Noweda              | Clobetasol propionate | 11101312        | 1              |
| Gehe                | Clobetasol propionate | 11300702        | 1              |
| Fagron              | Clobetasol propionate | 11300703        | 1              |
| Caelo               | Clobetasol propionate | 11300704        | 2              |
| Fagron              | Clobetasol propionate | 11D26-N04       | 1              |
| Anzag               | Clobetasol propionate | 11H10-N02       | 1              |
| Fagron              | Clobetasol propionate | 11H10-N02       | 1              |
| Gehe                | Clobetasol propionate | 11L12-N05       | 1              |
| Fagron              | Clobetasol propionate | 12/25-N01       | 1              |
| Euro OTC            | Clobetasol propionate | 1204037-01      | 1              |
| Euro OTC            | Clobetasol propionate | 12082013B       | 1              |
| Caesar u Loretz     | Clobetasol propionate | 12107608        | 2              |
| Euro OTC            | Clobetasol propionate | 12110-01        | 1              |

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| Supplier                   | Substance             | Batch            | Spectra |
|----------------------------|-----------------------|------------------|---------|
| Sanacorp                   | Clobetasol propionate | 1211021-01       | 1       |
| Gehe 02.07.2013            | Clobetasol propionate | 1211021-01       | 1       |
| euroho/gehe                | Clobetasol propionate | 1211021-01       | 1       |
| Fagron                     | Clobetasol propionate | 1211021-02       | 1       |
| Symbiotica Spec.           | Clobetasol propionate | 1211021-03       | 1       |
| symbiotica/gehe            | Clobetasol propionate | 1211021-03       | 1       |
| Caelo                      | Clobetasol propionate | 12342302         | 1       |
| Caesar/Lorenz              | Clobetasol propionate | 12342305         | 3       |
| Alliance                   | Clobetasol propionate | 12342305         | 1       |
| Phönix                     | Clobetasol propionate | 12342306         | 1       |
| Caesar & Loretz/ Noweda    | Clobetasol propionate | 12342306         | 1       |
| AHD, 24.05.2013            | Clobetasol propionate | 12342307         | 1       |
| Caelo                      | Clobetasol propionate | 12342307         | 1       |
| Caesar/Lorenz              | Clobetasol propionate | 12342309         | 1       |
| Caesar/Loretz              | Clobetasol propionate | 12342310         | 1       |
| Noweda                     | Clobetasol propionate | 12342310         | 1       |
| Caelo                      | Clobetasol propionate | 12342312         | 1       |
| Euro OTC                   | Clobetasol propionate | 12E08-N04        | 1       |
| Fagron                     | Clobetasol propionate | 12e08n04         | 1       |
| Fagron                     | Clobetasol propionate | 12E08-n04        | 1       |
| Gehe                       | Clobetasol propionate | 12E08-N04        | 1       |
| Caelo                      | Clobetasol propionate | 12J25-N01        | 1       |
| Gehe                       | Clobetasol propionate | 12J25-N01        | 1       |
| Euro OTC                   | Clobetasol propionate | 130604002        | 1       |
| Caelo                      | Clobetasol propionate | 13134703         | 3       |
| faragon                    | Clobetasol propionate | 13A02-N04        | 1       |
| Caelo                      | Clobetasol propionate | 13A02-N04        | 1       |
| Fagron                     | Clobetasol propionate | 13A02-N04        | 1       |
| Fagron                     | Clobetasol propionate | 13G23-N01NT0421M | 1       |
| Fagron                     | Clobetasol propionate | 13G23N01         | 1       |
| Fagron                     | Clobetasol propionate | 13G23-N01        | 1       |
| Caelo                      | Clobetasol propionate | 15031401         | 1       |
| Euro OTC                   | Clobetasol propionate | 2405212835       | 1       |
| Caelo                      | Clobetasol propionate | 24081302         | 1       |
| Caelo                      | Clobetasol propionate | 31071302         | 1       |
| Caelo                      | Clobetasol propionate | 36/AKD2          | 1       |
| Fagron                     | Clobetasol propionate | 3713M-02835      | 1       |
| Phoenix 29.11.12           | Clobetasol propionate | 700225           | 2       |
| Alliance Health 17.01.2... | Clobetasol propionate | APB00547/112010C | 1       |
| Crystal Pharma             | Clobetasol propionate | C0054/1          | 1       |
| Euro OTC                   | Clobetasol propionate | CL0-BL2153/0711  | 1       |
| Symbiotica Spec./Phönix    | Clobetasol propionate | CL0-B12153/0711  | 1       |
| Fagron                     | Clobetasol propionate | NS0292-M         | 1       |
| Fagron                     | Clobetasol propionate | NR0671M          | 1       |
| Noweda                     | Clobetasol propionate | NR0671M          | 1       |
| noweda                     | Clobetasol propionate | 1004036-03       | 1       |
| Symbiotica                 | Clobetasol propionate | 121021-01        | 1       |
| Sanacorp                   | Clobetasol propionate | 12107609         | 2       |
| Bombastus                  | Clobetasol propionate | 12342303         | 1       |
| Sanacorp                   | Clobetasol propionate | 12342310         | 1       |
| Caelo                      | Clobetasol propionate | 14102416         | 1       |

- 68 676 spectra from 413 *Apo-Ident* customers from a total of 23 574 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).



## Validation results

The validation runs checked whether the substance/substance group *Clobetasol propionate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Clobetasol propionate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 466           | 0              | 70 920        |
| <b>Type B</b> | 0              | 462           | 44             | 146 223       |
| <b>Type C</b> | 0              | 931           | 26             | 68 676        |

The substance/substance group *Clobetasol propionate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.7124 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 91.3043 % (> 90.7115 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 97.2832 % (> 96.9697 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21092     | 21092               | 0.00                         | 15.90                           |
| 21473     | 21473               | 0.00                         | 22.72                           |
| 21611     | 21611               | 0.00                         | 24.05                           |
| 21802     | 21802               | 0.00                         | 39.33                           |
| 21896     | 21896               | 0.00                         | 23.90                           |
| 22714     | 22714               | 0.00                         | 17.58                           |
| 22724     | 21092               | 2.62                         | 13.71                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Clonidine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20637-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Clonidine hydrochloride; Clonidini hydrochloridum; Clonidinum hydrochloricum

### Special notes

When selecting the *Clonidine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Clonidine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Clonidine hydroc... | 13I25-B07        | 21220     | 40      | 20131009    |
| Fagron   | Clonidine hydroc... | 14H11-B04-311163 | 22967     | 40      | 20140929    |
| Fagron   | Clonidine hydroc... | 15L11-B01-332270 | 23228     | 40      | 1709153     |
| Fagron   | Clonidine hydroc... | 14H11-B04-311163 | 22967SI   | 40      | 20140929    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Clonidine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 322 spectra of 7 reference samples from the substance/substance group *Clonidine hydrochloride*.

| Supplier | Substance               | Batch            | Sample ID    | Spectra |
|----------|-------------------------|------------------|--------------|---------|
| Fagron   | Clonidine hydrochloride | 12A03-N04        | 20637        | 40      |
| Fagron   | Clonidine hydrochloride | 14H11-B04-311163 | 21966        | 60      |
| Fagron   | Clonidine hydrochloride | 15L11-B01-332270 | 23410        | 40      |
| Fagron   | Clonidine hydrochloride | 14H11-B04-311163 | not required | 42      |
| Fagron   | Clonidine hydrochloride | 14H11-B04-311163 | 21966SI      | 60      |
| Fagron   | Clonidine hydrochloride | 15L11-B01-332270 | 23228SI      | 40      |
| Fagron   | Clonidine hydrochloride | 15L11-B01-332270 | 23410SI      | 40      |

- 146 407 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Clonidine hydrochloride*.

| Supplier | Substance               | Batch            | Spectra |
|----------|-------------------------|------------------|---------|
| Fagron   | Clonidine hydrochloride | 14H11-B04-298642 | 1       |

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Clonidine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Clonidine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 280           | 42             | 146 407       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Clonidine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 86.9565 % (> 86.0248 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21220     | 23228               | 9.86                         | 52.37                           |
| 22967     | 23228               | 1.54                         | 48.02                           |
| 23228     | 23228               | 0.00                         | 46.69                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Clotrimazole**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20000-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Clotrimazole; Clotrimazolum

### Special notes

When selecting the *Clotrimazole* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Clotrimazole*:

| Supplier | Substance    | Batch      | Sample ID | Spectra | Certificate |
|----------|--------------|------------|-----------|---------|-------------|
| Fagron   | Clotrimazole | 12I21-N01  | 20794     | 40      | 20120322    |
| Caelo    | Clotrimazole | 13184113   | 21087     | 40      | 20130614    |
| Caelo    | Clotrimazole | 13224204   | 21114     | 40      | 20130815    |
| Euro OTC | Clotrimazole | 1306036-01 | 21207     | 40      | 20130823    |
| Fagron   | Clotrimazole | 14B05-B36  | 21259     | 40      | 20140225    |

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| Supplier | Substance    | Batch     | Sample ID | Spectra | Certificate |
|----------|--------------|-----------|-----------|---------|-------------|
| Fagron   | Clotrimazole | 14C04-B31 | 21264     | 40      | 20140319    |
| Caelo    | Clotrimazole | 13224220  | 21352     | 40      | 20130815    |
| Euro OTC | Clotrimazole | 1510003   | 22229     | 40      | 20151111*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 320 spectra of 8 reference samples from the substance/substance group *Clotrimazole*. These samples are listed above in the [calibration samples](#) section.
- 71 066 spectra from a total of 1544 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 7 reference samples from the substance/substance group *Clotrimazole*.

| Supplier | Substance    | Batch    | Sample ID          | Spectra |
|----------|--------------|----------|--------------------|---------|
| Caelo    | Clotrimazole | 91457249 | 20000              | 30      |
| Caelo    | Clotrimazole | 12320815 | 20861              | 30      |
| Caelo    | Clotrimazole | 13224220 | 21353              | 40      |
| Euro OTC | Clotrimazole | 1510003  | 22229 <sup>†</sup> | 20      |
| Euro OTC | Clotrimazole | 1607046  | 22793              | 40      |
| Euro OTC | Clotrimazole | 1703028  | 23129              | 40      |
| Caelo    | Clotrimazole | 171116   | 23322              | 40      |

- 146 489 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B*

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1457 spectra from 327 *Apo-Ident* customers from 302 batches from the substance/substance group *Clotrimazole*.

| Supplier                    | Substance    | Batch       | Spectra |
|-----------------------------|--------------|-------------|---------|
| Caelo                       | Clotrimazole | 1170717     | 1       |
| Euro OTC                    | Clotrimazole | 6051501     | 1       |
| hochhaus-Apotheke           | Clotrimazole | 916A-01276  | 1       |
| Sanacorp                    | Clotrimazole | 105/AKD1    | 1       |
| Caelo                       | Clotrimazole | 108/AKD1    | 1       |
| Sanacorp                    | Clotrimazole | 109/AKD3    | 1       |
| Sanacorp                    | Clotrimazole | 109/AKD6    | 1       |
| Caelo                       | Clotrimazole | 110/AKD7    | 1       |
| Caelo                       | Clotrimazole | 110/AKD8    | 1       |
| Caelo                       | Clotrimazole | 110/AKD9    | 1       |
| Pharmachem.Pöckneck/Phoe... | Clotrimazole | 12100039-02 | 1       |
| Euro OTC                    | Clotrimazole | 121003901   | 3       |
| Euro OTC                    | Clotrimazole | 1210039-01  | 27      |
| Euro OTC                    | Clotrimazole | 1210039-02  | 22      |
| EuRho/Phoenix               | Clotrimazole | 1210039-02  | 1       |
| Fagron                      | Clotrimazole | 1210039-02  | 1       |
| Caelo                       | Clotrimazole | 12159902    | 15      |
| Caelo                       | Clotrimazole | 12320809    | 4       |
| Caelo                       | Clotrimazole | 123456      | 1       |
| Fagron                      | Clotrimazole | 12E02-N12   | 10      |
| Fagron                      | Clotrimazole | 12E30-N02   | 1       |
| Euro OTC                    | Clotrimazole | 1306036     | 2       |
| Caelo                       | Clotrimazole | 1306036     | 1       |
| Caelo                       | Clotrimazole | 1306036-01  | 5       |
| Euro OTC                    | Clotrimazole | 1306036-01  | 43      |
| Euro OTC                    | Clotrimazole | 130603601   | 3       |
| AHD 31.07.2014 EK:6,96      | Clotrimazole | 1306036-01  | 1       |
| Euro OTC                    | Clotrimazole | 130636-01   | 2       |
| Euro OTC                    | Clotrimazole | 1309034-01  | 19      |
| Fagron                      | Clotrimazole | 1309034-01  | 3       |
| Alliance Healthcare         | Clotrimazole | 1309034-01  | 1       |
| Euro OTC                    | Clotrimazole | 130903401   | 3       |
| Gehe                        | Clotrimazole | 1309034-01  | 2       |
| Caelo                       | Clotrimazole | 1309034-01  | 1       |
| Euro OTC                    | Clotrimazole | 1309034-02  | 22      |
| EuRho                       | Clotrimazole | 1309034-02  | 1       |
| Euro OTC                    | Clotrimazole | 130903402   | 1       |
| Caelo                       | Clotrimazole | 1309034-02  | 3       |
| Phoenix 23.10.14 5,50       | Clotrimazole | 1309034-02  | 1       |
| Phoenix                     | Clotrimazole | 1309034-02  | 1       |
| Euro OTC                    | Clotrimazole |             | 1       |
| Caelo                       | Clotrimazole | 1309034-C1  | 1       |
| Euro OTC                    | Clotrimazole | 1309054-02  | 1       |
| Euro OTC                    | Clotrimazole | 1314Q1276   | 1       |
| Caelo                       | Clotrimazole | 132234216   | 1       |
| Caelo                       | Clotrimazole | 13224201    | 26      |
| Caelo                       | Clotrimazole | 13224204    | 3       |
| Caelo                       | Clotrimazole | 13224210    | 14      |
| Sino Phyto                  | Clotrimazole | 13224210    | 2       |

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| Supplier                   | Substance    | Batch           | Spectra |
|----------------------------|--------------|-----------------|---------|
| Caelo                      | Clotrimazole | 13224211        | 6       |
| Caelo                      | Clotrimazole | 13224212        | 10      |
| gehe                       | Clotrimazole | 13224212        | 1       |
| Sanacorp                   | Clotrimazole | 13224214        | 2       |
| Caelo                      | Clotrimazole | 13224214        | 11      |
| Caelo                      | Clotrimazole | 13224215        | 3       |
| Caelo                      | Clotrimazole | 13224216        | 12      |
| Caelo                      | Clotrimazole | 13224217        | 11      |
| Noweda                     | Clotrimazole | 13224217        | 1       |
| Caelo                      | Clotrimazole | 13224218        | 14      |
| Caelo                      | Clotrimazole | 13224219        | 7       |
| Sanacorp                   | Clotrimazole | 13224219        | 1       |
| Caelo                      | Clotrimazole | 13224220        | 6       |
| Caelo                      | Clotrimazole | 13224221        | 3       |
| Vdl 14.07.14               | Clotrimazole | 13224225        | 1       |
| Caelo                      | Clotrimazole | 13224225        | 3       |
| Euro OTC                   | Clotrimazole | 1409027         | 5       |
| Caelo                      | Clotrimazole | 13324204        | 1       |
| Euro OTC                   | Clotrimazole | 1409027-01      | 24      |
| Euro OTC                   | Clotrimazole | 140902701       | 2       |
| EuRho                      | Clotrimazole | 1409027-01      | 2       |
| EuRho/Phoenix              | Clotrimazole | 1409027-01      | 1       |
| Euro OTC                   | Clotrimazole | 1409027-02      | 32      |
| Euroo / Phönix             | Clotrimazole | 1409027-02      | 1       |
| Caelo                      | Clotrimazole | 1409027-02      | 2       |
| Euro OTC                   | Clotrimazole | 140902702       | 2       |
| Fagron                     | Clotrimazole | 1409027-02      | 1       |
| Euro OTC                   | Clotrimazole | 1409027-02Mg10g | 1       |
| Euro OTC                   | Clotrimazole | 1409027-03      | 11      |
| Caelo                      | Clotrimazole | 1409027-03      | 2       |
| EuroTOC / Noweda           | Clotrimazole | 1409027-03      | 1       |
| Guangzhou Hanpu Pharmac... | Clotrimazole | 1409027-03      | 1       |
| Euro OTC                   | Clotrimazole | 1409027-04      | 20      |
| Caelo                      | Clotrimazole | 1409027-04      | 1       |
| Dr. Wolff                  | Clotrimazole | 1409027-04      | 2       |
| Euro OTC                   | Clotrimazole | 140927-01       | 1       |
| Caelo                      | Clotrimazole | 14144905        | 17      |
| Sanacorp                   | Clotrimazole | 14144905        | 1       |
| VDI 27.10.14 27,30 Euro    | Clotrimazole | 14144905        | 2       |
| Caelo                      | Clotrimazole | 14144911        | 12      |
| Caelo                      | Clotrimazole | 14144912        | 2       |
| Caelo                      | Clotrimazole | 14144913        | 2       |
| Noweda 07.07.2015          | Clotrimazole | 14144913        | 1       |
| Caelo                      | Clotrimazole | 14144914        | 5       |
| Euro OTC                   | Clotrimazole | 14144914        | 1       |
| Caelo                      | Clotrimazole | 14144917        | 7       |
| Caelo                      | Clotrimazole | 14144918        | 14      |
| sanacorp                   | Clotrimazole | 14144918        | 1       |
| Caelo                      | Clotrimazole | 14337801        | 12      |
| Fagron                     | Clotrimazole | 14223201        | 1       |
| Berkel AHK                 | Clotrimazole | 14337801        | 1       |
| A.H.D.                     | Clotrimazole | 14337801        | 1       |
| Noweda                     | Clotrimazole | 14337801        | 1       |
| Caelo                      | Clotrimazole | 14337802        | 9       |
| Caelo                      | Clotrimazole | 14337807        | 8       |
| VDL;11.06.15;27,90EUR      | Clotrimazole | 14337807        | 1       |
| AHD/Hedinger               | Clotrimazole | 14337807        | 1       |
| Caesar&Loretz GmbH/Anzag   | Clotrimazole | 14337807        | 1       |
| Caelo                      | Clotrimazole | 14337809        | 14      |
| Caelo                      | Clotrimazole | 14337811        | 4       |

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| <b>Supplier</b>    | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|--------------------|------------------|-------------------|----------------|
| Phönix Gotha       | Clotrimazole     | 14337811          | 1              |
| Caelo              | Clotrimazole     | 14337812          | 5              |
| Caelo              | Clotrimazole     | 14337813          | 6              |
| Caelo              | Clotrimazole     | 14337814          | 6              |
| Caesar&Loretz GmbH | Clotrimazole     | 14337814          | 1              |
| Caello/Anzag       | Clotrimazole     | 14337815          | 1              |
| Caelo              | Clotrimazole     | 14337815          | 6              |
| Caelo              | Clotrimazole     | 14337816          | 12             |
| Noweda             | Clotrimazole     | 14337816          | 1              |
| Caelo              | Clotrimazole     | 14337817          | 11             |
| Sanacorp           | Clotrimazole     | 14337817          | 1              |
| Caelo              | Clotrimazole     | 14337818          | 9              |
| Fagron             | Clotrimazole     | 14337818          | 1              |
| wepa/Sanaco        | Clotrimazole     | 14337819          | 1              |
| Caelo              | Clotrimazole     | 14337819          | 3              |
| Euro OTC           | Clotrimazole     | 14337819          | 1              |
| Caelo              | Clotrimazole     | 14337824          | 1              |
| Caelo              | Clotrimazole     | 14337827          | 5              |
| Caelo              | Clotrimazole     | 14337828          | 7              |
| Caelo              | Clotrimazole     | 14337829          | 23             |
| Caelo              | Clotrimazole     | 14337830          | 2              |
| Caelo              | Clotrimazole     | 14337832          | 1              |
| Fagron             | Clotrimazole     | 14B05-B35         | 2              |
| Caelo              | Clotrimazole     | 14B05-B35         | 1              |
| Fagron             | Clotrimazole     | 14B05-B35-293542  | 3              |
| Fagron             | Clotrimazole     | 14B05-B35-293544  | 5              |
| Fagron             | Clotrimazole     | 14B05-B35-294932  | 1              |
| Fagron             | Clotrimazole     | 14B05-B35-294935  | 3              |
| Fagron             | Clotrimazole     | 14B05B35294935    | 1              |
| Fagron             | Clotrimazole     | 14B05-B35-299941  | 2              |
| Fagron             | Clotrimazole     | 14b05-b35-299941  | 1              |
| Fagron             | Clotrimazole     | 14B05-B36         | 8              |
| Apomix             | Clotrimazole     | 14B05-B36         | 1              |
| Fagron             | Clotrimazole     | 14B05-B36-291165  | 3              |
| Fagron             | Clotrimazole     | 14b05b36291166    | 1              |
| Fagron             | Clotrimazole     | 14b05-b36-291166  | 1              |
| Fagron             | Clotrimazole     | 14B05-B36-291166  | 2              |
| Fagron             | Clotrimazole     | 14B05-B36-291167  | 7              |
| Caelo              | Clotrimazole     | 14B05-B36-291167  | 1              |
| Caelo              | Clotrimazole     | 14B05-B36-291168  | 2              |
| Fagron             | Clotrimazole     | 14B05-B36-2991166 | 1              |
| Fagron             | Clotrimazole     | 14B06-B06         | 1              |
| Fagron             | Clotrimazole     | 14B06-B06-299942  | 1              |
| Fagron             | Clotrimazole     | 14B06-B06-299943  | 5              |
| Fagron             | Clotrimazole     | 14C04-B30-291656  | 8              |
| Fagron             | Clotrimazole     | 14C04-B30         | 2              |
| Caelo              | Clotrimazole     | 14c04-b30-291656  | 1              |
| Caelo              | Clotrimazole     | 14C04-B30-291656  | 2              |
| Fagron             | Clotrimazole     | 14C04-B30-291661  | 2              |
| Fagron             | Clotrimazole     | 14C04-B31         | 9              |
| Phoenix            | Clotrimazole     | 14c04b31          | 1              |
| Fagron             | Clotrimazole     | 14C04B31          | 1              |
| Caelo              | Clotrimazole     | 14c04-B31         | 1              |
| Euro OTC           | Clotrimazole     | 14C04-B31-291660  | 1              |
| Fagron             | Clotrimazole     | 14C04-B31-291660  | 2              |
| Fagron             | Clotrimazole     | 14C04-B31-294939  | 7              |
| Caelo              | Clotrimazole     | 14C04-B31-294939  | 1              |
| Fagron             | Clotrimazole     | 14C04-B31-294940  | 1              |
| Gehe               | Clotrimazole     | 14C04-B31-294952  | 1              |
| Fagron             | Clotrimazole     | 14C04-B31-294952  | 1              |

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| Supplier                   | Substance    | Batch            | Spectra |
|----------------------------|--------------|------------------|---------|
| Fagron                     | Clotrimazole | 14C04-B31-299954 | 7       |
| Caelo                      | Clotrimazole | 14C04B31-299954  | 1       |
| Caelo                      | Clotrimazole | 14C04-B31-299955 | 1       |
| Fagron                     | Clotrimazole | 14C04-B31-299955 | 1       |
| Fagron                     | Clotrimazole | 14C04-B31-299959 | 1       |
| Fagron                     | Clotrimazole | 14C04-B31-299960 | 6       |
| Fagron                     | Clotrimazole | 14C04-B32        | 2       |
| Fagron                     | Clotrimazole | 14C04B32291657   | 1       |
| Caelo                      | Clotrimazole | 14C04-B32-291657 | 1       |
| Caelo                      | Clotrimazole | 150003-02        | 1       |
| Euro OTC                   | Clotrimazole | 15042014C        | 1       |
| Euro OTC                   | Clotrimazole | 15072014A        | 1       |
| Euro OTC                   | Clotrimazole | 1510003-01       | 25      |
| Caelo                      | Clotrimazole | 1510003-01       | 2       |
| Guangzhou Hanpu Pharmac... | Clotrimazole | 1510003-01       | 1       |
| Fagron                     | Clotrimazole | 1510003-01       | 1       |
| Euro OTC                   | Clotrimazole | 1510003-02       | 11      |
| Guangzhou Hanpu Pharmac... | Clotrimazole | 1510003-02       | 1       |
| Caelo                      | Clotrimazole | 15395602         | 13      |
| Euro OTC                   | Clotrimazole | 151003-01        | 1       |
| Caelo                      | Clotrimazole | 15395603         | 4       |
| Caelo                      | Clotrimazole | 15395604         | 9       |
| Euro OTC                   | Clotrimazole | 15395604         | 1       |
| Caelo                      | Clotrimazole | 15395605         | 5       |
| Caelo                      | Clotrimazole | 1539561          | 1       |
| Anzag                      | Clotrimazole | 15395610         | 1       |
| Caelo                      | Clotrimazole | 15395610         | 2       |
| Caelo                      | Clotrimazole | 15395611         | 8       |
| Caelo                      | Clotrimazole | 15395613         | 3       |
| Caesar u Loretz            | Clotrimazole | 15395613         | 1       |
| caesar&lorenz GmbH,Phön... | Clotrimazole | 15395614         | 1       |
| Caelo                      | Clotrimazole | 15395614         | 4       |
| Caelo                      | Clotrimazole | 15395615         | 4       |
| Caelo                      | Clotrimazole | 15395617         | 7       |
| Hedinger/Alliance H.       | Clotrimazole | 15395617         | 1       |
| Caelo                      | Clotrimazole | 15395618         | 9       |
| Phönix                     | Clotrimazole | 15395618         | 1       |
| Caelo                      | Clotrimazole | 15395623         | 1       |
| Caelo                      | Clotrimazole | 15395604         | 1       |
| Fagron                     | Clotrimazole | 15C14-B05-311100 | 1       |
| Fagron                     | Clotrimazole | 15G14-B05        | 3       |
| Gehe                       | Clotrimazole | 15G14-B05        | 1       |
| Fagron                     | Clotrimazole | 15G14-B05-311100 | 7       |
| Caelo                      | Clotrimazole | 15G14-B05-311101 | 1       |
| Fagron                     | Clotrimazole | 15G14-B05-311102 | 1       |
| Fagron                     | Clotrimazole | 15G14-B05-311103 | 5       |
| apomix/Phönix              | Clotrimazole | 15G14-B05-311103 | 3       |
| Fagron                     | Clotrimazole | 15G14-B06        | 2       |
| Caelo                      | Clotrimazole | 15G14-B05-316483 | 1       |
| Fagron                     | Clotrimazole | 15g14-b06-311054 | 1       |
| Fagron                     | Clotrimazole | 15G14-B06-311054 | 3       |
| Caelo                      | Clotrimazole | 15G14-B06-311054 | 1       |
| Fagron                     | Clotrimazole | 15G14B06311054   | 1       |
| Fagron                     | Clotrimazole | 15G14-B06-311055 | 1       |
| Caelo                      | Clotrimazole | 15G14-B06-311057 | 1       |
| AHD 27.10 Ek.7,07          | Clotrimazole | 1607046          | 1       |
| Euro OTC                   | Clotrimazole | 1607046          | 1       |
| Euro OTC                   | Clotrimazole | 1607046-0        | 1       |
| Euro OTC                   | Clotrimazole | 1607046-01       | 24      |
| Bombastus                  | Clotrimazole | 1607046-01       | 2       |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|----------------------------|------------------|-------------------|----------------|
| Caelo                      | Clotrimazole     | 1607046-01        | 1              |
| Fagron                     | Clotrimazole     | 1607046-02        | 1              |
| Euro OTC                   | Clotrimazole     | 1607046-02        | 5              |
| Caelo                      | Clotrimazole     | 1607046-02        | 2              |
| EuRho/ Phoenix             | Clotrimazole     | 160704602         | 1              |
| Caesar u Loretz            | Clotrimazole     | 16234501          | 1              |
| Euro OTC                   | Clotrimazole     | 1607064-01        | 1              |
| Caelo                      | Clotrimazole     | 16234501          | 3              |
| Caelo                      | Clotrimazole     | 16234502          | 2              |
| Caelo                      | Clotrimazole     | 16234503          | 2              |
| Caelo                      | Clotrimazole     | 16234504          | 3              |
| Caelo                      | Clotrimazole     | 16234505          | 5              |
| Phönix                     | Clotrimazole     | 16234505          | 1              |
| Caelo                      | Clotrimazole     | 16234509          | 2              |
| Caesar&Loretz GmbH,15.0... | Clotrimazole     | 16234509          | 1              |
| Caelo                      | Clotrimazole     | 16234511          | 3              |
| Fargon                     | Clotrimazole     | 16234511          | 1              |
| Caelo                      | Clotrimazole     | 16234513          | 1              |
| Fagron                     | Clotrimazole     | 16B09-B06-311507  | 2              |
| Noweda                     | Clotrimazole     | 16234511          | 1              |
| Gehe                       | Clotrimazole     | 16234513          | 1              |
| Caelo                      | Clotrimazole     | 16234515          | 1              |
| Fagron                     | Clotrimazole     | 16B09-B06-311506  | 1              |
| Fagron                     | Clotrimazole     | 16B09-B06         | 1              |
| Fagron                     | Clotrimazole     | 16B09-B06-311785  | 2              |
| Euro OTC                   | Clotrimazole     | 16B11-B04-320088  | 1              |
| Fagron                     | Clotrimazole     | 16B11-B04-320088  | 2              |
| Fagron                     | Clotrimazole     | 16B11-B04-327611  | 1              |
| Fagron                     | Clotrimazole     | 16E20-B10-321598  | 3              |
| Fargron / Noweda           | Clotrimazole     | 16E20-B10-324555  | 1              |
| Fagron                     | Clotrimazole     | 16E20-B10-327349  | 1              |
| Fagron                     | Clotrimazole     | 16E20-B10-32197   | 1              |
| Fagron                     | Clotrimazole     | 16E20-B10-324555  | 1              |
| Fagron                     | Clotrimazole     | 16J07-B02-330216  | 1              |
| Caelo                      | Clotrimazole     | 17011601          | 1              |
| Euro OTC                   | Clotrimazole     | 1703028-01        | 5              |
| Alliance/Euro              | Clotrimazole     | 1703028-01        | 1              |
| Oberlinden Apotheke        | Clotrimazole     | 201401300378      | 2              |
| Fagron                     | Clotrimazole     | 17A19-B04332114   | 1              |
| Euro OTC                   | Clotrimazole     | 21052015B         | 1              |
| Euro OTC                   | Clotrimazole     | 22122014B         | 1              |
| Euro OTC                   | Clotrimazole     | 2214A-01276       | 1              |
| Caelo                      | Clotrimazole     | 418072-1-P        | 1              |
| Euro OTC                   | Clotrimazole     | 23121408          | 1              |
| Euro OTC                   | Clotrimazole     | 700135            | 2              |
| Caelo                      | Clotrimazole     | 415050-2-P        | 1              |
| Audor Pharma               | Clotrimazole     | APCLT/1703/0016CC | 1              |
| Audor Pharma               | Clotrimazole     | AP1306036-01C     | 1              |
| Caelo                      | Clotrimazole     |                   | 6              |
| Fagron                     | Clotrimazole     | CLT/1307/0065A    | 2              |
| Fagron                     | Clotrimazole     | CLT/1604/00227A   | 1              |
| Caelo                      | Clotrimazole     | Fagron            | 1              |
| Caelo                      | Clotrimazole     | 311111            | 1              |
| Noweda                     | Clotrimazole     | 10247316          | 1              |
| Caelo                      | Clotrimazole     | 1882321           | 1              |
| Euro OTC                   | Clotrimazole     | 1006044-02        | 1              |
| Fagron                     | Clotrimazole     | 9041304           | 1              |
| Caelo                      | Clotrimazole     | 10247328          | 3              |
| Gehe                       | Clotrimazole     | 10247328          | 1              |
| Kehr                       | Clotrimazole     | 10247331          | 1              |

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| <b>Supplier</b>    | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|--------------------|------------------|--------------|----------------|
| Kehr               | Clotrimazole     | 10247332     | 2              |
| Caelo              | Clotrimazole     | 10247332     | 1              |
| Caelo              | Clotrimazole     | 11/22-N10    | 1              |
| Euro OTC           | Clotrimazole     | 1105014-01   | 1              |
| Euro OTC           | Clotrimazole     | 1105014-02   | 3              |
| Caelo              | Clotrimazole     | 1105014-02   | 1              |
| Euro OTC           | Clotrimazole     | 110501402    | 1              |
| Phönix Gotha       | Clotrimazole     | 1108053-01   | 2              |
| Euro OTC           | Clotrimazole     | 1108053-01   | 5              |
| Gehe               | Clotrimazole     | 1108053-01   | 1              |
| Euro OTC           | Clotrimazole     | 110805301    | 1              |
| Euro OTC           | Clotrimazole     | 1108053-02   | 6              |
| Caelo              | Clotrimazole     | 1108053-02   | 1              |
| Phönix Gotha       | Clotrimazole     | 1108053-02   | 2              |
| EuRho              | Clotrimazole     | 1108053-02   | 1              |
| Caelo              | Clotrimazole     | 11081201     | 1              |
| Fagron             | Clotrimazole     | 11101209     | 1              |
| Caelo              | Clotrimazole     | 11305505     | 2              |
| Caelo              | Clotrimazole     | 11305506     | 3              |
| Caelo              | Clotrimazole     | 11305507     | 2              |
| Caelo              | Clotrimazole     | 11305513     | 9              |
| phönix             | Clotrimazole     | 11305513     | 1              |
| Caelo              | Clotrimazole     | 11305511     | 1              |
| Fagron             | Clotrimazole     | 11E17-N10    | 3              |
| Fagron             | Clotrimazole     | 11D01-N06    | 1              |
| Fagron             | Clotrimazole     | 11A05-N14    | 1              |
| Caelo              | Clotrimazole     | 11-K21-N19   | 1              |
| Fagron             | Clotrimazole     | 11G15-N10    | 1              |
| Gehe               | Clotrimazole     | 11K21-N19    | 2              |
| Fagron             | Clotrimazole     | 11K21-N19    | 1              |
| Fagron             | Clotrimazole     | 11k21-n19    | 1              |
| Noweda             | Clotrimazole     | 11K21-N19    | 2              |
| Fagron             | Clotrimazole     | 11L12-N10    | 5              |
| FARGON             | Clotrimazole     | 11112-n10    | 1              |
| Fagron             | Clotrimazole     | 12/21-N01    | 5              |
| Großhandel         | Clotrimazole     | 12/21-N04    | 1              |
| Fagron             | Clotrimazole     | 12/21-N04    | 4              |
| Euro OTC           | Clotrimazole     | 1203040      | 1              |
| Anzag, 12.11.2012  | Clotrimazole     | 1203040      | 1              |
| Euro OTC           | Clotrimazole     | 1203040-01   | 3              |
| Europharm/Otto     | Clotrimazole     | 1203040-01   | 1              |
| Euro OTC           | Clotrimazole     | 1203040-02   | 10             |
| Europharm/Otto     | Clotrimazole     | 1203040-02   | 1              |
| Gehe               | Clotrimazole     | 1203040-02   | 1              |
| EuRho              | Clotrimazole     | 1203040-02   | 1              |
| Euro OTC           | Clotrimazole     | 1203040-03   | 10             |
| Sanacorp           | Clotrimazole     | 1203040-03   | 1              |
| Noweda             | Clotrimazole     | 1203040-03   | 2              |
| Anzag 30.01.2013   | Clotrimazole     | 1203040-03   | 2              |
| Gehe/EuRho         | Clotrimazole     | 1203040-03   | 1              |
| GEHE               | Clotrimazole     | 1203040-03   | 1              |
| Euro OTC           | Clotrimazole     | 12082013C    | 1              |
| Euro OTC           | Clotrimazole     | 1209211276   | 1              |
| Phönix             | Clotrimazole     | 1210039-01   | 1              |
| Fagron             | Clotrimazole     | 1210039-01   | 1              |
| Caelo              | Clotrimazole     | 1210039-01   | 1              |
| Euro/Noweda        | Clotrimazole     | 1210039-01   | 1              |
| Phönix, 28.10.2013 | Clotrimazole     | 1210039-02   | 1              |
| Gehe               | Clotrimazole     | 121003902    | 1              |
| Caelo              | Clotrimazole     | 1210039-02   | 1              |

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| <b>Supplier</b>             | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|-----------------------------|------------------|--------------|----------------|
| EuRho/Phönix                | Clotrimazole     | 1210039-2    | 1              |
| Stumpf                      | Clotrimazole     | 12159902     | 1              |
| Sanacorp                    | Clotrimazole     | 12159902     | 1              |
| Caelo                       | Clotrimazole     | 12159904     | 2              |
| Kehr                        | Clotrimazole     | 12159904     | 1              |
| Caelo                       | Clotrimazole     | 12159911     | 2              |
| Phönix/ henry lamotte       | Clotrimazole     | 12159911     | 1              |
| Caelo                       | Clotrimazole     | 12159913     | 9              |
| Caelo                       | Clotrimazole     | 12159916     | 6              |
| Fagron                      | Clotrimazole     |              | 2              |
| Fagron                      | Clotrimazole     | 1221n04      | 1              |
| Caelo                       | Clotrimazole     | 1230809      | 1              |
| Sanacorp                    | Clotrimazole     | 1230805      | 1              |
| Fagron                      | Clotrimazole     | 1221N04      | 1              |
| Caelo                       | Clotrimazole     | 12320805     | 4              |
| Caelo                       | Clotrimazole     | 12320806     | 6              |
| Caelo                       | Clotrimazole     | 12320807     | 5              |
| Caelo                       | Clotrimazole     | 12320808     | 11             |
| phönix                      | Clotrimazole     | 12320809     | 1              |
| Caelo                       | Clotrimazole     | 12320813     | 3              |
| Caelo                       | Clotrimazole     | 12320814     | 10             |
| Caesar/Lorenz               | Clotrimazole     | 12320814     | 1              |
| Bombastus                   | Clotrimazole     | 12320815     | 1              |
| Caelo                       | Clotrimazole     | 12320815     | 3              |
| Caelo                       | Clotrimazole     | 1234567      | 1              |
| Caelo                       | Clotrimazole     | 1259913      | 1              |
| Fagron                      | Clotrimazole     | 12A05-N10    | 6              |
| Fagron                      | Clotrimazole     | 12a05-n10    | 1              |
| Phoenix                     | Clotrimazole     | 12A05-N10    | 1              |
| Fagron                      | Clotrimazole     | 12B27-N05    | 4              |
| Caelo                       | Clotrimazole     | 12B27-N05    | 2              |
| Noweda                      | Clotrimazole     | 12E02-N12    | 1              |
| Fagron                      | Clotrimazole     | 12e02-N12    | 1              |
| Caelo                       | Clotrimazole     | 12E02-N12    | 2              |
| Fagron                      | Clotrimazole     | 12E30-N07    | 13             |
| Fiebig 10.06.13 ek: 8,58EUR | Clotrimazole     | 12E30-N07    | 1              |
| Caelo                       | Clotrimazole     | 12E30-N07    | 1              |
| Fagron                      | Clotrimazole     | 12F02-N12    | 1              |
| Fagron                      | Clotrimazole     | 12I16-N04    | 1              |
| Euro OTC                    | Clotrimazole     | 12I21-N01    | 1              |
| Fagron                      | Clotrimazole     | 12I21-N01    | 7              |
| Fagron                      | Clotrimazole     | 12I21-N04    | 8              |
| Fagron                      | Clotrimazole     | 12I21N04     | 1              |
| FARGON                      | Clotrimazole     | 12i21-n04    | 1              |
| Caelo                       | Clotrimazole     | 12I21-N04    | 1              |
| anzag,18.01.2013            | Clotrimazole     | 12I21-N04    | 1              |
| Fagron                      | Clotrimazole     | 12K15-N01    | 1              |
| Fagron                      | Clotrimazole     | 12I21-N04    | 2              |
| Fagron                      | Clotrimazole     | 12I21-n04    | 1              |
| FARGON                      | Clotrimazole     | 12I21-n04    | 1              |
| Gehe/EuRho                  | Clotrimazole     | 12o3040-03   | 1              |
| EuRho                       | Clotrimazole     | 1306036-01   | 2              |
| Gehe                        | Clotrimazole     | 1306036-01   | 4              |
| Großhandel                  | Clotrimazole     | 1306036-01   | 1              |
| PHOENIX am 22.01.2014       | Clotrimazole     | 1306036-01   | 1              |
|                             | Clotrimazole     | 1306036-01   | 1              |
| Caelo                       | Clotrimazole     | 13148007     | 1              |
| Caelo                       | Clotrimazole     | 13184103     | 13             |
| Gehe                        | Clotrimazole     | 13184103     | 1              |
| Caelo                       | Clotrimazole     | 13184105     | 15             |

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| Supplier                 | Substance    | Batch            | Spectra |
|--------------------------|--------------|------------------|---------|
| Sanacorp                 | Clotrimazole | 13184105         | 1       |
| Europ Ots Pharma         | Clotrimazole | 13184105         | 1       |
| Caelo                    | Clotrimazole | 13184111         | 7       |
| Caesar&Loretz GmbH/Anzag | Clotrimazole | 13184111         | 1       |
| Caelo                    | Clotrimazole | 131841111        | 1       |
| Caelo                    | Clotrimazole | 13184113         | 4       |
| Noweda                   | Clotrimazole | 13224201         | 1       |
| Gehe                     | Clotrimazole | 13224216         | 1       |
| Phoenix                  | Clotrimazole | 13224215         | 1       |
| Fagron                   | Clotrimazole | 13C25-N10        | 11      |
| Euro OTC                 | Clotrimazole | 14090027-01      | 1       |
| Phönix                   | Clotrimazole | 13C25-N10        | 1       |
| Caesar&Loretz,Phoenix    | Clotrimazole | 14144912         | 1       |
| Phönix                   | Clotrimazole | 14337809         | 1       |
| Fagron                   | Clotrimazole | 14Coa-B30-291656 | 1       |
| Fagron                   | Clotrimazole | 20110113         | 1       |
| Fagron                   | Clotrimazole | 20111018         | 4       |
| Caelo                    | Clotrimazole | 20111018         | 1       |
| Fischar/Gehe             | Clotrimazole | 20111018         | 1       |
| Sanacorp                 | Clotrimazole | 20111018         | 1       |
| Caelo                    | Clotrimazole | 20111115         | 1       |
| Euro OTC                 | Clotrimazole | 20111115         | 1       |
| Noweda                   | Clotrimazole | 20111115         | 1       |
| Fagron                   | Clotrimazole | 20120603         | 4       |
| Caelo                    | Clotrimazole | 20130207         | 1       |
| Fagron                   | Clotrimazole | 20151112-3       | 1       |
| Euro OTC                 | Clotrimazole | 21122013A        | 1       |
| Euro OTC                 | Clotrimazole | 2313M01276       | 1       |
| Euro OTC                 | Clotrimazole | 30011402         | 1       |
| Caelo                    | Clotrimazole | 26071305         | 1       |
| Caelo                    | Clotrimazole | 3513M-01276      | 1       |
| Fagron                   | Clotrimazole | 4812E-01276 (NP) | 1       |
| Euro OTC                 | Clotrimazole | 3912E-01276      | 1       |
| Caelo                    | Clotrimazole | 412091-2-P       | 1       |
| Caelo                    | Clotrimazole | 700135-0006      | 1       |
| Fagron                   | Clotrimazole | C22H17CIN2       | 1       |
| Gehe                     | Clotrimazole | 12/21-N01        | 1       |
| EUro/AHD                 | Clotrimazole | 1210039-01       | 2       |
| Sanacorp                 | Clotrimazole | 12320814         | 1       |
| Fagron                   | Clotrimazole | 12b27-n05        | 1       |
| Fagron                   | Clotrimazole | 12E02N12         | 1       |
| Anzag                    | Clotrimazole | 12I21-N04        | 1       |
| europharma               | Clotrimazole | 1306036-01       | 1       |
| AHD                      | Clotrimazole | 13184105         | 1       |
| Fagron                   | Clotrimazole | 13224201         | 1       |

- 68 176 spectra from 414 *Apo-Ident* customers from a total of 23 503 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Clotrimazole* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose,



all relevant spectra of the various substances were compared with *Clotrimazole* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 320           | 0              | 71 066        |
| <b>Type B</b> | 0              | 240           | 0              | 146 489       |
| <b>Type C</b> | 0              | 1432          | 25             | 68 176        |

The substance/substance group *Clotrimazole* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.1250 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 98.2841 % (> 98.0782 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20794     | 22229               | 2.21                         | 44.87                           |
| 21087     | 22229               | 2.74                         | 46.13                           |
| 21114     | 22229               | 3.44                         | 45.26                           |
| 21207     | 22229               | 5.09                         | 43.83                           |
| 21259     | 22229               | 5.31                         | 40.06                           |
| 21264     | 22229               | 5.07                         | 41.19                           |
| 21352     | 22229               | 3.55                         | 45.25                           |
| 22229     | 22229               | 0.00                         | 48.21                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Colistin sulfate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20318-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Colistin sulfate; Colistin sulphate; Colistini sulfas; Colistinum sulfuricum

### Special notes

When selecting the *Colistin sulfate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Colistin sulfate*:

| Supplier | Substance        | Batch      | Sample ID | Spectra | Certificate |
|----------|------------------|------------|-----------|---------|-------------|
| Fagron   | Colistin sulfate | 13G05-N01  | 20915     | 40      | 20130719    |
| Fagron   | Colistin sulfate | 14E02-B03  | 21346     | 40      | 1501654     |
| Euro OTC | Colistin sulfate | 1406001-01 | 21619     | 40      | 1508600     |
| Euro OTC | Colistin sulfate | 1507044    | 21852     | 40      | 20150817*   |
| Euro OTC | Colistin sulfate | 1602021    | 22371     | 40      | 20160307*   |

*continued on the next page*

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| Supplier | Substance        | Batch            | Sample ID | Spectra | Certificate |
|----------|------------------|------------------|-----------|---------|-------------|
| Euro OTC | Colistin sulfate | 1606008          | 22695     | 40      | 20160704*   |
| Fagron   | Colistin sulfate | 16F03-B01-324216 | 22973     | 40      | 20160706    |
| Audor    | Colistin sulfate | APKB-CS-1603034C | 23026     | 40      | 20160627    |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 320 spectra of 8 reference samples from the substance/substance group *Colistin sulfate*. These samples are listed above in the [calibration samples](#) section.
- 71 066 spectra from a total of 1544 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 305 spectra of 9 reference samples from the substance/substance group *Colistin sulfate*.

| Supplier     | Substance        | Batch            | Sample ID          | Spectra |
|--------------|------------------|------------------|--------------------|---------|
| Fagron       | Colistin sulfate | 7I18-N05         | 20318              | 40      |
| Fagron       | Colistin sulfate | 13G05-N01        | 21209              | 40      |
| Euro OTC     | Colistin sulfate | 1406001-01       | 21619 <sup>†</sup> | 20      |
| Euro OTC     | Colistin sulfate | 1406002-01       | 21700              | 45      |
| Euro OTC     | Colistin sulfate | 1507044          | 21852 <sup>†</sup> | 20      |
| Euro OTC     | Colistin sulfate | 1602021          | 22371 <sup>†</sup> | 20      |
| Audor Pharma | Colistin sulfate | APKB-CS-1602026C | 22974              | 40      |
| Audor Pharma | Colistin sulfate | APKB-CS-1602026C | 23027              | 40      |
| Euro OTC     | Colistin sulfate | 1709009          | 23616              | 40      |

- 146 424 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 8 spectra from 3 *Apo-Ident* customers from 7 batches from the substance/substance group *Colistin sulfate*.

| Supplier     | Substance        | Batch            | Spectra |
|--------------|------------------|------------------|---------|
| Euro OTC     | Colistin sulfate | 1507044-01       | 1       |
| Fagron       | Colistin sulfate | 15E15-B01-315340 | 1       |
| Euro OTC     | Colistin sulfate | 1606008-01       | 1       |
| Fagron       | Colistin sulfate | 16F03-B01        | 1       |
| Fagron       | Colistin sulfate | 16J03-B10        | 1       |
| Audor Pharma | Colistin sulfate | APKB-CS-1601026C | 1       |
| Audor Pharma | Colistin sulfate | APKB-CS-1603034C | 2       |

- 69 625 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Colistin sulfate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Colistin sulfate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 320           | 0              | 71 066        |
| <b>Type B</b> | 0              | 265           | 40             | 146 424       |
| <b>Type C</b> | 0              | 8             | 0              | 69 625        |

The substance/substance group *Colistin sulfate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.1250 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 86.8852 % (> 85.9016 %)  |
| <b>Type C</b> | 100.0000 % (> 99.9814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to

exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20915     | 21619               | 4.84                         | 25.76                           |
| 21346     | 21346               | 0.00                         | 26.92                           |
| 21619     | 21619               | 0.00                         | 26.54                           |
| 21852     | 21852               | 0.00                         | 26.00                           |
| 22371     | 22371               | 0.00                         | 24.48                           |
| 22695     | 22695               | 0.00                         | 28.19                           |
| 22973     | 21852               | 2.15                         | 24.79                           |
| 23026     | 21346               | 13.59                        | 27.04                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Colophony**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20627-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Colophony; Colophonium

### Special notes

When selecting the *Colophony* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Colophony*:

| Supplier | Substance | Batch    | Sample ID | Spectra | Certificate        |
|----------|-----------|----------|-----------|---------|--------------------|
| Caelo    | Colophony | 12301410 | 21782     | 40      | AR-15-FG-016314-01 |
| Caelo    | Colophony | 15186804 | 21971     | 40      | AR-16-FG-005931-01 |
| Caelo    | Colophony | 161332   | 22588     | 40      | 20160510*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Colophony*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 88 spectra of 4 reference samples from the substance/substance group *Colophony*.

| Supplier | Substance | Batch    | Sample ID          | Spectra |
|----------|-----------|----------|--------------------|---------|
| Caelo    | Colophony | 10147506 | 20627              | 40      |
| Caelo    | Colophony | 12301410 | 21782 <sup>†</sup> | 20      |
| Caelo    | Colophony | 15186804 | 21971 <sup>†</sup> | 20      |
| Caelo    | Colophony | 15186807 | not required       | 8       |

- 146 641 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Colophony*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Colophony* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Colophony* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 75            | 45             | 71 266        |
| <b>Type B</b> | 0              | 57            | 31             | 146 641       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Colophony* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate        |
|---------------|--------------------------|-------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 62.5000 % (> 60.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 64.7727 % (> 61.3636 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)               |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21782     | 21782               | 0.00                         | 89.44                           |
| 21971     | 21971               | 0.00                         | 35.26                           |
| 22588     | 22588               | 0.00                         | 88.76                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Cyanocobalamin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21299-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Cyanocobalamin; Cyanocobalaminum

### Special notes

When selecting the *Cyanocobalamin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cyanocobalamin*:

| Supplier | Substance      | Batch      | Sample ID | Spectra | Certificate        |
|----------|----------------|------------|-----------|---------|--------------------|
| Caelo    | Cyanocobalamin | 13342803   | 21299     | 40      | AR-15-FG-005429-01 |
| Caelo    | Cyanocobalamin | 13342807   | 21479     | 40      | AR-15-FG-014917-01 |
| Euro OTC | Cyanocobalamin | 1305040-01 | 21635     | 40      | AR-15-FG-005214-01 |
| Euro OTC | Cyanocobalamin | 1506035    | 21867     | 40      | 20150708*          |
| Euro OTC | Cyanocobalamin | 1506035    | 21872     | 40      | 0000010479         |

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| Supplier | Substance      | Batch    | Sample ID | Spectra | Certificate        |
|----------|----------------|----------|-----------|---------|--------------------|
| Caelo    | Cyanocobalamin | 160154   | 22441     | 40      | 20160309*          |
| Euro OTC | Cyanocobalamin | 1604017  | 22536     | 30      | 20160509*          |
| Caelo    | Cyanocobalamin | 13342807 | 21479SI   | 20      | AR-15-FG-014917-01 |
| Euro OTC | Cyanocobalamin | 1506035  | 21867SI   | 40      | 20150708*          |
| Euro OTC | Cyanocobalamin | 1506035  | 21872SI   | 30      | 0000010479         |
| Caelo    | Cyanocobalamin | 160154   | 22441SI   | 40      | 20160309*          |
| Euro OTC | Cyanocobalamin | 1604017  | 22536SI   | 30      | 20160509*          |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 430 spectra of 12 reference samples from the substance/substance group *Cyanocobalamin*. These samples are listed above in the *calibration samples* section.
- 70956 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this *chemometric model*, the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in *Appendix A*. The samples in *Appendix A* were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 245 spectra of 11 reference samples from the substance/substance group *Cyanocobalamin*.

| Supplier | Substance      | Batch      | Sample ID            | Spectra |
|----------|----------------|------------|----------------------|---------|
| Caelo    | Cyanocobalamin | 9351704    | 20858                | 40      |
| Caelo    | Cyanocobalamin | 13342807   | 21479 <sup>†</sup>   | 20      |
| Euro OTC | Cyanocobalamin | 1305040-01 | 21635 <sup>†</sup>   | 20      |
| Euro OTC | Cyanocobalamin | 1506035    | 21867 <sup>†</sup>   | 20      |
| Euro OTC | Cyanocobalamin | 1506035    | 21872 <sup>†</sup>   | 20      |
| Caelo    | Cyanocobalamin | 160154     | 22441 <sup>†</sup>   | 20      |
| Caelo    | Cyanocobalamin | 13342807   | 21479SI <sup>†</sup> | 40      |
| Euro OTC | Cyanocobalamin | 1506035    | 21867SI <sup>†</sup> | 20      |
| Euro OTC | Cyanocobalamin | 1506035    | 21872SI <sup>†</sup> | 15      |
| Caelo    | Cyanocobalamin | 160154     | 22441SI <sup>†</sup> | 20      |
| Euro OTC | Cyanocobalamin | 1604017    | 22536SI <sup>†</sup> | 10      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*).

- 146 484 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 20 spectra from 14 *Apo-Ident* customers from 15 batches from the substance/substance group *Cyanocobalamin*.

| Supplier                     | Substance      | Batch            | Spectra |
|------------------------------|----------------|------------------|---------|
| Fagron                       | Cyanocobalamin | 13I24-B01-292062 | 1       |
| Caelo                        | Cyanocobalamin | 14183301         | 1       |
| Fagron                       | Cyanocobalamin | 15F25-B05        | 1       |
| Caelo                        | Cyanocobalamin | 1604017-01       | 1       |
| Euro OTC                     | Cyanocobalamin | 5061204          | 1       |
| Caesar & Loretz GmbH, 4. . . | Cyanocobalamin | 9324102          | 1       |
| Caelo                        | Cyanocobalamin | 9351704          | 1       |
| Fagron                       | Cyanocobalamin | 10K02-N05        | 4       |
| Fagron                       | Cyanocobalamin | 10K02-N05        | 1       |
| Fagron                       | Cyanocobalamin | 13I24-B01-292062 | 1       |
| Caelo                        | Cyanocobalamin | 9336904          | 1       |
| Caelo                        | Cyanocobalamin | 9336907          | 1       |
| Caelo                        | Cyanocobalamin | 9373503          | 2       |
| Fagron                       | Cyanocobalamin | 15H31-B02-315113 | 1       |
| Caelo                        | Cyanocobalamin | 9324113          | 1       |
| Caelo                        | Cyanocobalamin | 9324102          | 1       |

- 69 613 spectra from 414 *Apo-Ident* customers from a total of 23 786 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cyanocobalamin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cyanocobalamin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 430           | 0              | 70 956        |
| <b>Type B</b> | 0              | 245           | 0              | 146 484       |
| <b>Type C</b> | 0              | 13            | 7              | 69 613        |

Hence, these spectra are not independent and are not of *Type B*.

The substance/substance group *Cyanocobalamin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.6047 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5510 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 65.0000 % (> 50.0000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21299            | 21299                      | 0.00                                | 17.10                                  |
| 21479            | 21479                      | 0.00                                | 26.79                                  |
| 21635            | 21635                      | 0.00                                | 22.16                                  |
| 21867            | 21867                      | 0.00                                | 21.83                                  |
| 21872            | 21872                      | 0.00                                | 29.29                                  |
| 22441            | 22441                      | 0.00                                | 28.17                                  |
| 22536            | 22536                      | 0.00                                | 33.05                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Cyproterone acetate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20593-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Cyproterone acetate; Cyproteroni acetat; Cyproteronum aceticum

### Special notes

When selecting the *Cyproterone acetate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cyproterone acetate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Cyproterone acet... | 13C11-N02        | 21262     | 40      | 1501534     |
| Fagron   | Cyproterone acet... | 13J16-No4        | 21985     | 55      | 1602654     |
| Fagron   | Cyproterone acet... | 15I11-B01-322117 | 22665     | 40      | 20150921    |
| Euro OTC | Cyproterone acet... | 1611003          | 22875     | 40      | 20161201*   |
| Fagron   | Cyproterone acet... | 17D11-B07-333693 | 23238     | 40      | 20170501    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 215 spectra of 5 reference samples from the substance/substance group *Cyproterone acetate*. These samples are listed above in the [calibration samples](#) section.
- 71 171 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 206 spectra of 7 reference samples from the substance/substance group *Cyproterone acetate*.

| Supplier | Substance           | Batch            | Sample ID          | Spectra |
|----------|---------------------|------------------|--------------------|---------|
| Fagron   | Cyproterone acetate | 12B14-N06        | 20593              | 40      |
| Fagron   | Cyproterone acetate | 11L22-N02        | 20603              | 40      |
| Fagron   | Cyproterone acetate | 13J16-No4        | 21985 <sup>†</sup> | 20      |
| Fagron   | Cyproterone acetate | 13J16-No4        | 21985SI            | 23      |
| Fagron   | Cyproterone acetate | 15I11-B01-322117 | 22665SI            | 33      |
| Euro OTC | Cyproterone acetate | 1611003          | 22875SI            | 30      |
| Fagron   | Cyproterone acetate | 17D11-B07-333693 | 23238SI            | 20      |

- 146 523 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 29 spectra from 17 *Apo-Ident* customers from 19 batches from the substance/substance group *Cyproterone acetate*.

| Supplier     | Substance           | Batch            | Spectra |
|--------------|---------------------|------------------|---------|
| Fagron       | Cyproterone acetate | 8B11-N06         | 1       |
| Fagron       | Cyproterone acetate | 12L19-N05        | 2       |
| Fagron       | Cyproterone acetate | 13/09-N03        | 1       |
| Fagron       | Cyproterone acetate | 13/16-N04        | 2       |
| Fagron       | Cyproterone acetate | 13I09-N03        | 1       |
| Fagron       | Cyproterone acetate | 13J16-N04        | 4       |
| Fagron       | Cyproterone acetate | 13j16n04         | 1       |
| Fagron       | Cyproterone acetate | 15I11-B01        | 1       |
| Fagron       | Cyproterone acetate | 16K09-B04        | 1       |
| Ebert-Jacobi | Cyproterone acetate | 16K09-B04-329036 | 1       |
| Audor Pharma | Cyproterone acetate | APCPA140201CP    | 1       |
| Fagron       | Cyproterone acetate | APCPA130201C     | 1       |
| Caelo        | Cyproterone acetate | B0392/110020     | 3       |
| Fagron       | Cyproterone acetate | B0392/110020     | 2       |
| Caelo        | Cyproterone acetate | CPA150301        | 1       |
| Fagron       | Cyproterone acetate | 12D02-N13        | 1       |
| Fagron       | Cyproterone acetate | 11L22-N02        | 1       |
| Fagron       | Cyproterone acetate | EU-CPA-170301    | 1       |
| Fagron       | Cyproterone acetate | 12F25-N09        | 2       |
| Fagron       | Cyproterone acetate | 12J24-N02        | 1       |

- 69 604 spectra from 414 *Apo-Ident* customers from a total of 23 782 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cyproterone acetate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cyproterone acetate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 215           | 0              | 71 171        |
| <b>Type B</b> | 0              | 177           | 29             | 146 523       |
| <b>Type C</b> | 0              | 19            | 10             | 69 604        |

The substance/substance group *Cyproterone acetate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.2093 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 85.9223 % (> 84.4660 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 65.5172 % (> 55.1724 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21262     | 21262               | 0.00                         | 39.68                           |
| 21985     | 21985               | 0.00                         | 41.78                           |
| 22665     | 21985               | 7.51                         | 41.84                           |
| 22875     | 22875               | 0.00                         | 39.14                           |
| 23238     | 21985               | 7.31                         | 38.50                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | Cysteine hydrochloride monohydrate                              |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20530-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Cysteine hydrochloride monohydrate; Cysteinum hydrochloricum

### Special notes

When selecting the *Cysteine hydrochloride monohydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                            |
|-------------------|------------------------------------------------------------|
| 978-3-7692-5416-7 | European Pharmacopoeia 8th Edition, Basic Version 2014 [3] |
| Komm2.2.40        | Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident [4]          |
| AA004             | Erstellung und Validierung eines IdentModul-Updates        |
| Anhang F          | Zusatz zu den Modellen der zweiten Stufe                   |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cysteine hydrochloride monohydrate*:

| Supplier | Substance             | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------------------|------------|-----------|---------|-------------|
| Euro OTC | Cysteine hydroch. ... | 1304019-01 | 21325     | 30      | 20130517    |
| Euro OTC | Cysteine hydroch. ... | 1507006    | 21840     | 40      | 20150713*   |
| Euro OTC | Cysteine hydroch. ... | 1701012    | 23003     | 40      | 20170207*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 110 spectra of 3 reference samples from the substance/substance group *Cysteine hydrochloride monohydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 276 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 290 spectra of 8 reference samples from the substance/substance group *Cysteine hydrochloride monohydrate*.

| Supplier | Substance                       | Batch      | Sample ID          | Spectra |
|----------|---------------------------------|------------|--------------------|---------|
| Dr. Behr | Cysteine hydrochloride monoh... | P-07014800 | 20422              | 40      |
| Euro OTC | Cysteine hydrochloride monoh... | 1112015-01 | 20530              | 40      |
| Euro OTC | Cysteine hydrochloride monoh... | 1112015-02 | 20630              | 40      |
| Euro OTC | Cysteine hydrochloride monoh... | 1304019-01 | 21325 <sup>†</sup> | 10      |
| Euro OTC | Cysteine hydrochloride monoh... | 1507006    | 21840 <sup>†</sup> | 20      |
| Euro OTC | Cysteine hydrochloride monoh... | 1510015    | 21941              | 60      |
| Euro OTC | Cysteine hydrochloride monoh... | 1603018    | 22516              | 40      |
| Euro OTC | Cysteine hydrochloride monoh... | 1706023    | 23548              | 40      |

- 146 439 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 17 spectra from 4 *Apo-Ident* customers from 7 batches from the substance/substance group *Cysteine hydrochloride monohydrate*.

| Supplier | Substance                       | Batch       | Spectra |
|----------|---------------------------------|-------------|---------|
| Euro OTC | Cysteine hydrochloride monoh... | 1311040-01  | 2       |
| Euro OTC | Cysteine hydrochloride monoh... | 1408003-01  | 4       |
| Euro OTC | Cysteine hydrochloride monoh... | 14080031-01 | 1       |
| Euro OTC | Cysteine hydrochloride monoh... | 1112015-01  | 2       |
| Euro OTC | Cysteine hydrochloride monoh... | 1206015-01  | 2       |
| Euro OTC | Cysteine hydrochloride monoh... | 1304019-01  | 5       |
| Euro OTC | Cysteine hydrochloride monoh... | 1603018-01  | 1       |

- 69 616 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cysteine hydrochloride monohydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cysteine hydrochloride monohydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 110           | 0              | 71 276        |
| <b>Type B</b> | 0              | 257           | 33             | 146 439       |
| <b>Type C</b> | 0              | 16            | 1              | 69 616        |

The substance/substance group *Cysteine hydrochloride monohydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.5455 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 88.6207 % (> 87.5862 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21325     | 21840               | 2.24                         | 13.34                           |
| 21840     | 21840               | 0.00                         | 10.60                           |
| 23003     | 23003               | 0.00                         | 7.22                            |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Cystine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20515-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Cystine; Cystinum

### Special notes

When selecting the *Cystine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Cystine*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Euro OTC | Cystine   | 1307052-01 | 21328     | 40      | 20130918    |
| Euro OTC | Cystine   | 1408016-01 | 21715     | 40      | 20140911    |
| Euro OTC | Cystine   | 1603010    | 22523     | 40      | 20160406*   |
| Euro OTC | Cystine   | 1610013    | 22863     | 40      | 20161110*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Cystine*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *Cystine*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Euro OTC | Cystine   | 1104017-01 | 20515              | 40      |
| Euro OTC | Cystine   | 1408016-01 | 21715 <sup>†</sup> | 20      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 9 spectra from 3 *Apo-Ident* customers from 6 batches from the substance/substance group *Cystine*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier | Substance | Batch            | Spectra |
|----------|-----------|------------------|---------|
| Euro OTC | Cystine   | 2081301          | 1       |
| Euro OTC | Cystine   | 3021502          | 1       |
| Euro OTC | Cystine   | 1204090          | 1       |
| Euro OTC | Cystine   | 1207013-01       | 3       |
| Fagron   | Cystine   | 12D26-B04-285823 | 2       |
| Euro OTC | Cystine   | 26081408         | 1       |

- 69 624 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Cystine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Cystine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 9             | 0              | 69 624        |

The substance/substance group *Cystine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21328     | 22523               | 5.60                         | 39.40                           |
| 21715     | 22523               | 5.25                         | 41.20                           |
| 22523     | 22523               | 0.00                         | 43.84                           |
| 22863     | 22863               | 0.00                         | 44.67                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Dapsone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22489-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Dapsone; Dapsonum

### Special notes

When selecting the *Dapsone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Dapsone*:

| Supplier | Substance | Batch    | Sample ID | Spectra | Certificate |
|----------|-----------|----------|-----------|---------|-------------|
| Caelo    | Dapsone   | 160735   | 22489     | 40      | 20160405*   |
| Caelo    | Dapsone   | 16073502 | 22736     | 40      | 20160405    |
| Caelo    | Dapsone   | 170311   | 23301     | 39      | 20170221*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 119 spectra of 3 reference samples from the substance/substance group *Dapsone*. These samples are listed above in the [calibration samples](#) section.
- 71 267 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *Dapsone*.

| Supplier | Substance | Batch    | Sample ID          | Spectra |
|----------|-----------|----------|--------------------|---------|
| Caelo    | Dapsone   | 160735   | 22489 <sup>†</sup> | 20      |
| Caelo    | Dapsone   | 16073502 | 22577              | 40      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Dapsone*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Dapsone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Dapsone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 119           | 0              | 71 267        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Dapsone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.9580 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22489     | 22489               | 0.00                         | 101.58                          |
| 22736     | 23301               | 10.21                        | 96.61                           |
| 23301     | 23301               | 0.00                         | 93.87                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Deoxycholic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20412-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Deoxycholic acid; Deoxycholic acidum

### Special notes

When selecting the *Deoxycholic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Deoxycholic acid*:

| Supplier | Substance        | Batch            | Sample ID | Spectra | Certificate        |
|----------|------------------|------------------|-----------|---------|--------------------|
| Fagron   | Deoxycholic acid | 14A02-B32-303429 | 21967     | 40      | AR-16-FG-004648-01 |
| Euro OTC | Deoxycholic acid | 1305051-01       | 22575     | 40      | 20130611           |
| Fagron   | Deoxycholic acid | 14A02-B32-303429 | 23014     | 40      | 20140116           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Deoxycholic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *Deoxycholic acid*.

| Supplier                     | Substance        | Batch            | Sample ID          | Spectra |
|------------------------------|------------------|------------------|--------------------|---------|
| New Zealand Pharmaceuti. . . | Deoxycholic acid | 411656           | 20412              | 40      |
| New Zealand Pharmaceuti. . . | Deoxycholic acid | 411656           | 20537              | 40      |
| Fagron                       | Deoxycholic acid | 14A02-B32-303429 | 21967 <sup>†</sup> | 20      |

- 146 629 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 7 spectra from 4 *Apo-Ident* customers from 7 batches from the substance/substance group *Deoxycholic acid*.

| Supplier        | Substance        | Batch     | Spectra |
|-----------------|------------------|-----------|---------|
| SAFICALCAN      | Deoxycholic acid | 413678    | 1       |
| GEHE 21.10.2014 | Deoxycholic acid | 13F13-N06 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



continued from previous page

| Supplier                   | Substance        | Batch      | Spectra |
|----------------------------|------------------|------------|---------|
| Fagron                     | Deoxycholic acid | 13J21-N14  | 1       |
| Gehe                       | Deoxycholic acid | 2012060253 | 1       |
| new zealand pharmaceuti... | Deoxycholic acid | 411656     | 1       |
| Fagron                     | Deoxycholic acid | 12L14-N07  | 1       |
| Euro OTC                   | Deoxycholic acid | 1305051-01 | 1       |

- 69 626 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Deoxycholic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Deoxycholic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 100           | 0              | 146 629       |
| <b>Type C</b> | 0              | 6             | 1              | 69 626        |

The substance/substance group *Deoxycholic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21967     | 21967               | 0.00                         | 35.65                           |
| 22575     | 21967               | 18.02                        | 35.17                           |
| 23014     | 21967               | 3.67                         | 36.23                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Dequalinium chloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20350-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Dequalinium chloride; Dequalinii chloridum; Dequalinium chloratum

### Special notes

When selecting the *Dequalinium chloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Dequalinium chloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Fagron   | Dequalinium chlo... | 11D29-N11  | 20660     | 80      | pending     |
| Fagron   | Dequalinium chlo... | 13I26-N10  | 21269     | 40      | 20130121    |
| Caelo    | Dequalinium chlo... | 12361908   | 21296     | 40      | 1412076     |
| Caelo    | Dequalinium chlo... | 12361906   | 21387     | 40      | 20121228    |
| Euro OTC | Dequalinium chlo... | 1405012-01 | 21617     | 40      | 20140623    |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Dequalinium chlo... | 1512032          | 22295     | 40      | 20160121*   |
| Caelo    | Dequalinium chlo... | 15218406         | 22953     | 40      | 20150622    |
| Caelo    | Dequalinium chlo... | 15402803         | 23121     | 40      | 1707614     |
| Fagron   | Dequalinium chlo... | 15B16-B04-332113 | 23266     | 40      | 20150226    |
| Caelo    | Dequalinium chlo... | 154028           | 23362     | 40      | 20160219*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 440 spectra of 10 reference samples from the substance/substance group *Dequalinium chloride*. These samples are listed above in the [calibration samples](#) section.
- 70 946 spectra from a total of 1542 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by †.

- 705 spectra of 15 reference samples from the substance/substance group *Dequalinium chloride*.

| Supplier | Substance            | Batch            | Sample ID          | Spectra |
|----------|----------------------|------------------|--------------------|---------|
| Caelo    | Dequalinium chloride | 9336412          | 20254              | 45      |
| Caelo    | Dequalinium chloride | 1166204          | 20350              | 40      |
| Caelo    | Dequalinium chloride | 11166203         | 20475              | 40      |
| Caelo    | Dequalinium chloride | 12077503         | 20716              | 40      |
| Caelo    | Dequalinium chloride | 12361906         | 21386              | 60      |
| Caelo    | Dequalinium chloride | 12361906         | 21387 <sup>†</sup> | 80      |
| Euro OTC | Dequalinium chloride | 1405012-01       | 21617 <sup>†</sup> | 20      |
| Euro OTC | Dequalinium chloride | 1512032          | 22295 <sup>†</sup> | 20      |
| Caelo    | Dequalinium chloride | 12361906         | 21386SI            | 60      |
| Caelo    | Dequalinium chloride | 12361906         | 21387SI            | 60      |
| Euro OTC | Dequalinium chloride | 1405012-01       | 21617SI            | 60      |
| Euro OTC | Dequalinium chloride | 1512032          | 22295SI            | 60      |
| Caelo    | Dequalinium chloride | 15218406         | 22953SI            | 40      |
| Fagron   | Dequalinium chloride | 15B16-B04-332113 | 23266SI            | 40      |
| Caelo    | Dequalinium chloride | 154028           | 23362SI            | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

- 146 024 spectra from a total of 3184 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 113 spectra from 81 *Apo-Ident* customers from 52 batches from the substance/substance group *Dequalinium chloride*.

| Supplier                | Substance            | Batch            | Spectra |
|-------------------------|----------------------|------------------|---------|
| Euro OTC                | Dequalinium chloride | 1210008-02       | 2       |
| Euro OTC                | Dequalinium chloride | 1405012-02       | 2       |
| Fagron                  | Dequalinium chloride | 12B14-N01        | 1       |
| Caelo                   | Dequalinium chloride | 13348805         | 2       |
| Euro OTC                | Dequalinium chloride | 1407029-02       | 3       |
| Caelo                   | Dequalinium chloride | 13A23-N02        | 1       |
| Fagron                  | Dequalinium chloride | 14C10-B03-292286 | 2       |
| Euro OTC                | Dequalinium chloride | 1512032-01       | 4       |
| Caelo                   | Dequalinium chloride | 15218401         | 5       |
| Lamotte/Spangroh        | Dequalinium chloride | 15218404         | 1       |
| Fag / Noweda            | Dequalinium chloride | 15B16-B04-321326 | 1       |
| Caelo                   | Dequalinium chloride | 215I-01325       | 1       |
| Caelo                   | Dequalinium chloride | 12077510         | 7       |
| LEBSA/Phoenix           | Dequalinium chloride | 1210008-03       | 1       |
| Caelo                   | Dequalinium chloride | 1210008-03       | 1       |
| Euro OTC                | Dequalinium chloride | 121000803        | 1       |
| S.Binder                | Dequalinium chloride | 1210008-04       | 1       |
| Caelo                   | Dequalinium chloride | 12361906         | 3       |
| Euro OTC                | Dequalinium chloride | 1210008-04       | 1       |
| Caelo                   | Dequalinium chloride | 12361908         | 3       |
| Caelo                   | Dequalinium chloride | 12361911         | 3       |
| Caelo                   | Dequalinium chloride | 13/26-N10        | 1       |
| Fagron                  | Dequalinium chloride | 13A23-N02        | 3       |
| Raben-Apotheke Mildenau | Dequalinium chloride | 1405012-01       | 1       |
| Fagron                  | Dequalinium chloride | 13I26-N10        | 1       |
| Euro OTC                | Dequalinium chloride | 1405012-01       | 4       |
| Lebsa/AHD               | Dequalinium chloride | 1405012-01       | 1       |
| Caelo                   | Dequalinium chloride | 1405012-02       | 1       |
| Euro OTC                | Dequalinium chloride | 1407029-01       | 4       |
| Fagron                  | Dequalinium chloride | 1407029-01       | 2       |
| Fagron                  | Dequalinium chloride | 14C10-B03        | 1       |
| Euro OTC                | Dequalinium chloride | 151203201        | 1       |
| Phönix                  | Dequalinium chloride | 151203201        | 1       |
| Gehe                    | Dequalinium chloride | 1512032-01       | 1       |
| Caelo                   | Dequalinium chloride | 15218402         | 1       |
| Caelo                   | Dequalinium chloride | 15218404         | 1       |
| Caelo                   | Dequalinium chloride | 15218406         | 1       |
| Caelo                   | Dequalinium chloride | 15218407         | 1       |
| Fagron                  | Dequalinium chloride | 15B16-B04        | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier         | Substance            | Batch            | Spectra |
|------------------|----------------------|------------------|---------|
| Fagron           | Dequalinium chloride | 15B16-B04-304432 | 1       |
| Caelo            | Dequalinium chloride | 3613A-01325      | 1       |
| Caelo            | Dequalinium chloride | 5315I-01325      | 1       |
| Fagron           | Dequalinium chloride |                  | 1       |
| Euro OTC         | Dequalinium chloride | 1210008-01       | 2       |
| Euro OTC         | Dequalinium chloride | 1010022-01       | 2       |
| Phönix           | Dequalinium chloride | 10127-N02Retest  | 1       |
| Fagron           | Dequalinium chloride | 10H05-N07        | 1       |
| Euro OTC         | Dequalinium chloride | 1110002-01       | 3       |
| EuRho            | Dequalinium chloride | 1110002-01       | 1       |
| Caelo            | Dequalinium chloride | 11166203         | 1       |
| Caelo            | Dequalinium chloride | 11166204         | 2       |
| Anzag ek:7.89EUR | Dequalinium chloride | 11166204         | 1       |
| Caelo            | Dequalinium chloride | 12077508         | 3       |
| Caelo            | Dequalinium chloride | 11166209         | 1       |
| Alliance Health  | Dequalinium chloride | 12077508         | 1       |
| AHD, 24.09.2013  | Dequalinium chloride | 12077508         | 1       |
| Euro OTC         | Dequalinium chloride | 1210008-03       | 2       |
| Noweda           | Dequalinium chloride | 12b14-n05        | 1       |
| Fagron           | Dequalinium chloride | 12B14-N05        | 1       |
| Fagron           | Dequalinium chloride | 12D05-N09        | 1       |
| Fagron           | Dequalinium chloride | 12G05-N07        | 2       |
| Caelo            | Dequalinium chloride | 12G05-N07        | 1       |
| Fagron           | Dequalinium chloride | 13D26-N06        | 3       |
| Euro OTC         | Dequalinium chloride | 15061204         | 1       |
| Caelo            | Dequalinium chloride | 220812K2         | 1       |
| GEHE             | Dequalinium chloride |                  | 1       |
| Euro OTC         | Dequalinium chloride | 1103045-01       | 1       |
| Caelo            | Dequalinium chloride |                  | 1       |

- 69 520 spectra from 414 *Apo-Ident* customers from a total of 23 749 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Dequalinium chloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Dequalinium chloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 409           | 31             | 70 946        |
| <b>Type B</b> | 0              | 493           | 212            | 146 024       |
| <b>Type C</b> | 0              | 93            | 20             | 69 520        |

The substance/substance group *Dequalinium chloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b> |
|---------------|--------------------------|-------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 92.9545 % (> 92.2727 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 69.9291 % (> 69.5035 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 82.3009 % (> 79.6460 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 20660            | 20660                      | 0.00                                | 72.90                                  |
| 21269            | 21296                      | 24.97                               | 42.29                                  |
| 21296            | 21296                      | 0.00                                | 33.32                                  |
| 21387            | 21296                      | 9.37                                | 43.54                                  |
| 21617            | 21296                      | 9.30                                | 44.17                                  |
| 22295            | 22295                      | 0.00                                | 44.73                                  |
| 22953            | 21296                      | 19.61                               | 40.22                                  |
| 23121            | 23121                      | 0.00                                | 57.00                                  |
| 23266            | 23362                      | 15.32                               | 49.19                                  |
| 23362            | 23362                      | 0.00                                | 46.16                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Dexamethasone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20009-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Dexamethasone; Dexamethasonum

### Special notes

When selecting the *Dexamethasone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Dexamethasone*:

| Supplier | Substance     | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------|------------------|-----------|---------|--------------------|
| Euro OTC | Dexamethasone | 1303007-01       | 21289     | 40      | 1407432            |
| Caelo    | Dexamethasone | 13084315         | 21403     | 40      | AR-15-FG-006810-01 |
| Euro OTC | Dexamethasone | 1601052          | 22364     | 30      | 20160225*          |
| Euro OTC | Dexamethasone | 1611001          | 22914     | 40      | 20161212*          |
| Fagron   | Dexamethasone | 16F02-B05-324844 | 23168     | 40      | 20160711           |
| Euro OTC | Dexamethasone | 1601052          | 22364SI   | 30      | 20160225*          |
| Euro OTC | Dexamethasone | 1611001          | 22914SI   | 37      | 20161212*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 257 spectra of 7 reference samples from the substance/substance group *Dexamethasone*. These samples are listed above in the [calibration samples](#) section.
- 71 129 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 530 spectra of 16 reference samples from the substance/substance group *Dexamethasone*.

| Supplier | Substance     | Batch            | Sample ID            | Spectra |
|----------|---------------|------------------|----------------------|---------|
| Caelo    | Dexamethasone | 81002179         | 20009                | 30      |
| Euro OTC | Dexamethasone | 1012005-01       | 20188                | 45      |
| Caelo    | Dexamethasone | 13084306         | 21062                | 40      |
| Euro OTC | Dexamethasone | 1209008-02       | 21078                | 40      |
| Caelo    | Dexamethasone | 13084315         | 21403 <sup>†</sup>   | 20      |
| Euro OTC | Dexamethasone | 1303007-01       | 21850                | 60      |
| Euro OTC | Dexamethasone | 1601052          | 22364 <sup>†</sup>   | 15      |
| Caelo    | Dexamethasone | 15054627         | 23169                | 40      |
| Caelo    | Dexamethasone | 171042           | 23331                | 40      |
| Euro OTC | Dexamethasone | 1708004          | 23692                | 40      |
| Euro OTC | Dexamethasone | 1303007-01       | 21850SI              | 45      |
| Euro OTC | Dexamethasone | 1601052          | 22364SI <sup>†</sup> | 15      |
| Fagron   | Dexamethasone | 16F02-B05-324844 | 23168SI              | 30      |
| Caelo    | Dexamethasone | 15054627         | 23169SI              | 20      |
| Caelo    | Dexamethasone | 171042           | 23331SI              | 24      |
| Euro OTC | Dexamethasone | 1708004          | 23692SI              | 26      |

- 146 199 spectra from a total of 3183 batches from further 862 substances. These spectra were

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 480 spectra from 198 *Apo-Ident* customers from 134 batches from the substance/substance group *Dexamethasone*.

| Supplier                | Substance     | Batch        | Spectra |
|-------------------------|---------------|--------------|---------|
| Phoenix Goettin         | Dexamethasone | 117113352302 | 1       |
| Euro OTC                | Dexamethasone | 10369920     | 2       |
| Caelo                   | Dexamethasone |              | 1       |
| Caelo                   | Dexamethasone | 10369921     | 2       |
| Fagron                  | Dexamethasone | 11D26-N10    | 4       |
| Caelo                   | Dexamethasone | 11D26-N10    | 1       |
| Fagron                  | Dexamethasone | 11L08-N01    | 4       |
| Caelo                   | Dexamethasone | 12033301     | 4       |
| Euro OTC                | Dexamethasone | 1209008-01   | 9       |
| Caelo                   | Dexamethasone | 12033315     | 4       |
| Euro OTC                | Dexamethasone | 1209008-02   | 26      |
| Euro OTC                | Dexamethasone | 120900802    | 2       |
| Fagron                  | Dexamethasone | 12B06-N12    | 6       |
| unbekannt               | Dexamethasone | 12D26-N09    | 1       |
| Euro OTC                | Dexamethasone | 13030007     | 1       |
| Euro OTC                | Dexamethasone | 13030007-01  | 1       |
| Euro OTC                | Dexamethasone | 1303007      | 1       |
| Raben-Apotheke Mildenau | Dexamethasone | 1303007-01   | 2       |
| Euro OTC                | Dexamethasone | 1303007-01   | 29      |
| Euro OTC                | Dexamethasone | 130300701    | 4       |
| Symbiotica              | Dexamethasone | 1303007-01   | 1       |
| EuRho                   | Dexamethasone | 1303007-01   | 1       |
| Euro OTC                | Dexamethasone | 130300702    | 2       |
| Euro OTC                | Dexamethasone | 1303007-02   | 6       |
| Euro OTC                | Dexamethasone | 1303007-03   | 16      |
| Caelo                   | Dexamethasone | 1303007-03   | 1       |
| GEHE 12.03.2014         | Dexamethasone | 13084306     | 1       |
| Henry Lamotte Oils GmbH | Dexamethasone | 13084304     | 1       |
| Caelo                   | Dexamethasone | 13084306     | 3       |
| Caelo                   | Dexamethasone | 13084307     | 3       |
| Fagron                  | Dexamethasone | 13084308     | 1       |
| Sanacorp                | Dexamethasone | 13084308     | 1       |
| Caelo                   | Dexamethasone | 13084308     | 2       |
| Caelo                   | Dexamethasone | 13084309     | 1       |
| Caelo                   | Dexamethasone | 13084310     | 6       |
| Gehe 8.04.2014          | Dexamethasone | 13084310     | 2       |
| Phoenix                 | Dexamethasone | 13084313     | 2       |
| Caelo                   | Dexamethasone | 13084313     | 3       |
| Caelo                   | Dexamethasone | 13084316     | 2       |
| Caelo                   | Dexamethasone | 13084317     | 6       |
| Gehe                    | Dexamethasone | 13084317     | 1       |
| Caelo                   | Dexamethasone | 13084319     | 2       |
| Caelo                   | Dexamethasone | 13084320     | 3       |
| Caelo                   | Dexamethasone | 1335213      | 1       |
| Caelo                   | Dexamethasone | 13352302     | 6       |
| Caelo                   | Dexamethasone | 13352304     | 1       |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------|------------------|----------------|
| Caelo                      | Dexamethasone    | 13352308         | 6              |
| Caelo                      | Dexamethasone    | 13352309         | 1              |
| Sanacorp                   | Dexamethasone    | 13352309         | 1              |
| Berkel AHK                 | Dexamethasone    | 13352309         | 1              |
| Caelo                      | Dexamethasone    | 13352310         | 5              |
| Euro OTC                   | Dexamethasone    | 13352309         | 1              |
| Phönix Gotha               | Dexamethasone    | 13352311         | 1              |
| Caelo                      | Dexamethasone    | 13352311         | 1              |
| Caelo                      | Dexamethasone    | 13352312         | 10             |
| Fagron                     | Dexamethasone    | 13D12-N19        | 1              |
| Caelo                      | Dexamethasone    | 13G08-N13        | 2              |
| Fagron                     | Dexamethasone    | 13G08-N13        | 5              |
| Phoenix                    | Dexamethasone    | 13g08n13         | 1              |
| Caelo                      | Dexamethasone    | 14196402         | 3              |
| Fagron                     | Dexamethasone    | 14A22-B03        | 2              |
| Fagron                     | Dexamethasone    | 14A22-B03-290700 | 1              |
| Fagron                     | Dexamethasone    | 14A22-B03-294030 | 1              |
| Fagron                     | Dexamethasone    | 14D11-B01        | 1              |
| Euro OTC                   | Dexamethasone    | 14D11-B01-294031 | 1              |
| Fagron                     | Dexamethasone    | 14D11-B01-294032 | 1              |
| Caleo                      | Dexamethasone    | 15054602         | 2              |
| Caelo                      | Dexamethasone    | 15054602         | 4              |
| Caelo                      | Dexamethasone    | 15054603         | 2              |
| Fagron                     | Dexamethasone    | 15054603         | 1              |
| Caelo                      | Dexamethasone    | 15054605         | 3              |
| Caelo                      | Dexamethasone    | 15054606         | 8              |
| Sanofi-Chimie FR/Noweda    | Dexamethasone    | 15054606         | 2              |
| Caesar&Loretz GmbH,Phön... | Dexamethasone    | 15054606         | 2              |
| Caelo                      | Dexamethasone    | 15054609         | 4              |
| Caelo                      | Dexamethasone    | 15054611         | 5              |
| Caelo                      | Dexamethasone    | 15054617         | 5              |
| Caelo                      | Dexamethasone    | 15054618         | 1              |
| Caelo                      | Dexamethasone    | 15054621         | 4              |
| Gehe                       | Dexamethasone    | 15054621         | 1              |
| Caelo                      | Dexamethasone    | 15054622         | 14             |
| caesar&loretz GmbH,Phön... | Dexamethasone    | 15054622         | 3              |
| Caelo                      | Dexamethasone    | 15054623         | 2              |
| Caelo                      | Dexamethasone    | 15054627         | 2              |
| Caelo                      | Dexamethasone    | 15054628         | 5              |
| Gehe                       | Dexamethasone    | 15054629         | 1              |
| Caelo                      | Dexamethasone    | 15054629         | 2              |
| Caelo                      | Dexamethasone    | 15054631         | 1              |
| Caelo                      | Dexamethasone    | 15215601         | 1              |
| Fagron                     | Dexamethasone    | 15A05-B01        | 1              |
| Fagron                     | Dexamethasone    | 15A05-B01-034636 | 1              |
| Fagron                     | Dexamethasone    | 15A05-B01-304636 | 2              |
| Fagron                     | Dexamethasone    | 15a05-b01-304636 | 1              |
| Caelo                      | Dexamethasone    | 15A05-B01-304637 | 1              |
| Fagron                     | Dexamethasone    | 15A05-B01-304637 | 1              |
| Fagron                     | Dexamethasone    | 15C16-B07        | 1              |
| Fagron                     | Dexamethasone    | 15C16-B07-308252 | 1              |
| Phoenix                    | Dexamethasone    | 15I04-B04        | 1              |
| Fagron                     | Dexamethasone    | 15I04-B04-315528 | 1              |
| PHÖNIX                     | Dexamethasone    | 15K17-B07        | 1              |
| Fagron                     | Dexamethasone    | 15K17-B07        | 1              |
| Euro OTC                   | Dexamethasone    | 1601052-01       | 12             |
| Sanacorp                   | Dexamethasone    | 1601052-01       | 1              |
| Euro OTC                   | Dexamethasone    | 1601052-02       | 6              |
| Symbiotica/Noweda          | Dexamethasone    | 1601052-02       | 1              |
| EuRho Anzag                | Dexamethasone    | 1601052-02       | 1              |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>   | <b>Spectra</b> |
|----------------------------|------------------|----------------|----------------|
| Caelo                      | Dexamethasone    | 1601052-02     | 1              |
| Euro OTC                   | Dexamethasone    | 1611001-01     | 4              |
| Euro OTC                   | Dexamethasone    | 161100101      | 2              |
| Ebert-Jacobi               | Dexamethasone    | 1611001-01     | 1              |
| Fagron                     | Dexamethasone    | 16F01-B05      | 1              |
| Fagron                     | Dexamethasone    | 2314A-01327    | 1              |
| Euro OTC                   | Dexamethasone    | alt2412A-01327 | 1              |
| Euro OTC                   | Dexamethasone    | DB003/0213     | 2              |
| Fagron                     | Dexamethasone    | 700107-0002    | 1              |
| Fagron                     | Dexamethasone    | 7H21N03        | 1              |
| Caelo                      | Dexamethasone    | 90939399       | 1              |
| Phönix Gotha               | Dexamethasone    | 9383629        | 1              |
| Caelo                      | Dexamethasone    | 9383631        | 1              |
| Fagron                     | Dexamethasone    | 9383631        | 1              |
| Caelo                      | Dexamethasone    | 10369917       | 1              |
| Caelo                      | Dexamethasone    | 10369919       | 1              |
| Phönix Gotha               | Dexamethasone    | 10369919       | 1              |
| Caelo                      | Dexamethasone    | 10369920       | 6              |
| ANZAG am 29.05.2012        | Dexamethasone    | 10369920       | 1              |
| Gehe                       | Dexamethasone    | 10369920       | 1              |
| Caesar & Loretz GmbH, 4... | Dexamethasone    | 10369922       | 1              |
| Phoenix                    | Dexamethasone    | 10369928       | 1              |
| Euro OTC                   | Dexamethasone    | 1107006-01     | 1              |
| Euro OTC                   | Dexamethasone    | 110700601      | 1              |
| Noweda                     | Dexamethasone    | 1107006-02     | 1              |
| Euro OTC                   | Dexamethasone    | 1111055-01     | 6              |
| Noweda                     | Dexamethasone    | 1111055-01     | 2              |
| Euro OTC                   | Dexamethasone    | 111105501      | 1              |
| Euro OTC                   | Dexamethasone    | 1111055-02     | 3              |
| Fagron                     | Dexamethasone    | 11F30-N02      | 1              |
| Euro OTC                   | Dexamethasone    | 12030320       | 1              |
| Euro OTC                   | Dexamethasone    | 1203032-01     | 6              |
| Anzag                      | Dexamethasone    | 1203032-01     | 1              |
| Phönix                     | Dexamethasone    | 120303201      | 1              |
| Fagron                     | Dexamethasone    | 1203032-02     | 1              |
| Euro OTC                   | Dexamethasone    | 1203032-02     | 4              |
| Caelo                      | Dexamethasone    | 12033304       | 1              |
| Caelo                      | Dexamethasone    | 12033305       | 4              |
| Anzag 18.06.2013           | Dexamethasone    | 12033305       | 1              |
| Phönix                     | Dexamethasone    | 12033306       | 1              |
| Caelo                      | Dexamethasone    | 12033307       | 6              |
| Caelo                      | Dexamethasone    | 12033306       | 1              |
| Caelo                      | Dexamethasone    | 12033308       | 2              |
| Sanofi-Chimie, FR/ Noweda  | Dexamethasone    | 12033308       | 1              |
| Caelo                      | Dexamethasone    | 12033312       | 1              |
| Caelo                      | Dexamethasone    | 12033314       | 7              |
| gehe 30.09.13              | Dexamethasone    | 12033314       | 2              |
| Phönix                     | Dexamethasone    | 12033314       | 1              |
| Phönix Gotha               | Dexamethasone    | 12033315       | 1              |
| GEHE                       | Dexamethasone    | 12033317       | 1              |
| Caelo                      | Dexamethasone    | 12033317       | 5              |
| Caelo                      | Dexamethasone    | 12033318       | 5              |
| Gehe                       | Dexamethasone    | 12033318       | 1              |
| Euro OTC                   | Dexamethasone    | 1209006-02     | 1              |
| Euro OTC                   | Dexamethasone    | 1209008        | 1              |
| Fagron                     | Dexamethasone    | 1209008-01     | 1              |
| Pharmacia&Upjohn Comp      | Dexamethasone    | 1209008-02     | 1              |
| Gehe                       | Dexamethasone    | 120900802      | 1              |
| Caelo                      | Dexamethasone    | 12091306       | 1              |
| Phönix 10.01.2013          | Dexamethasone    | 12165803       | 1              |

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| Supplier | Substance     | Batch             | Spectra |
|----------|---------------|-------------------|---------|
| Caelo    | Dexamethasone | 12165803          | 1       |
| Caelo    | Dexamethasone | 12165804          | 2       |
| Anzag    | Dexamethasone | 1233305           | 1       |
| Fagron   | Dexamethasone | 12D26-N09         | 2       |
| Fagron   | Dexamethasone | 12D26-NH09        | 1       |
| Fagron   | Dexamethasone | 12H21-N11         | 4       |
| Caelo    | Dexamethasone | 13084304          | 2       |
| Caelo    | Dexamethasone | 13084305          | 4       |
| Caelo    | Dexamethasone | 13084314          | 1       |
| Caelo    | Dexamethasone | 130854306         | 1       |
| Gehe     | Dexamethasone | 13D12-N09         | 2       |
| Fagron   | Dexamethasone | 13D12-N09         | 3       |
| Caelo    | Dexamethasone | 13D12-N09         | 1       |
| Euro OTC | Dexamethasone | 1512211327        | 1       |
| Caelo    | Dexamethasone | 3084310           | 1       |
| Euro OTC | Dexamethasone | 2803211327        | 1       |
| Euro OTC | Dexamethasone | 5213A1327         | 1       |
| Euro OTC | Dexamethasone |                   | 1       |
| Caelo    | Dexamethasone | 72134487          | 1       |
| Caelo    | Dexamethasone | DM-MIC10005K      | 1       |
| Fagron   | Dexamethasone | DZ11005K12B06-N12 | 1       |
| Euro OTC | Dexamethasone | DZ11005K          | 1       |
| Gehe     | Dexamethasone | 1203032-02        | 1       |

- 69 153 spectra from 414 *Apo-Ident* customers from a total of 23 667 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Dexamethasone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Dexamethasone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 257           | 0              | 71 129        |
| <b>Type B</b> | 0              | 520           | 10             | 146 199       |
| <b>Type C</b> | 0              | 471           | 9              | 69 153        |

The substance/substance group *Dexamethasone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.6654 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 98.1132 % (> 97.5472 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 98.1250 % (> 97.5000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several

new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21289     | 21289               | 0.00                         | 43.75                           |
| 21403     | 21403               | 0.00                         | 11.80                           |
| 22364     | 22364               | 0.00                         | 10.82                           |
| 22914     | 22914               | 0.00                         | 10.88                           |
| 23168     | 21289               | 7.61                         | 46.37                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Dexamethasone acetate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20313-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Dexamethasone acetate; Dexamethasoni acetas; Dexamethasonum aceticum

### Special notes

When selecting the *Dexamethasone acetate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Dexamethasone acetate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Caelo    | Dexamethasone ac... | 13260703   | 21301     | 40      | 1412430     |
| Caelo    | Dexamethasone ac... | 13260706   | 21593     | 40      | 1502537     |
| Euro OTC | Dexamethasone ac... | 1405024-01 | 21614     | 40      | 20140620    |
| Caelo    | Dexamethasone ac... | 14200207   | 21815     | 40      | 20140807    |
| Euro OTC | Dexamethasone ac... | 1405024-01 | 21614SI   | 30      | 20140620    |
| Caelo    | Dexamethasone ac... | 14200207   | 21815SI   | 30      | 20140807    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 220 spectra of 6 reference samples from the substance/substance group *Dexamethasone acetate*. These samples are listed above in the [calibration samples](#) section.
- 71 166 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 336 spectra of 11 reference samples from the substance/substance group *Dexamethasone acetate*.

| Supplier | Substance             | Batch      | Sample ID            | Spectra |
|----------|-----------------------|------------|----------------------|---------|
| Caelo    | Dexamethasone acetate | 11093210   | 20313                | 40      |
| Caelo    | Dexamethasone acetate | 10145912   | 20325                | 40      |
| Caelo    | Dexamethasone acetate | 13260706   | 21593 <sup>†</sup>   | 20      |
| Euro OTC | Dexamethasone acetate | 1405024-01 | 21614 <sup>†</sup>   | 20      |
| Caelo    | Dexamethasone acetate | 14200207   | 21815 <sup>†</sup>   | 20      |
| Caelo    | Dexamethasone acetate | 161066     | 22437                | 60      |
| Euro OTC | Dexamethasone acetate | 1708011    | 23693                | 40      |
| Euro OTC | Dexamethasone acetate | 1405024-01 | 21614SI <sup>†</sup> | 15      |
| Caelo    | Dexamethasone acetate | 14200207   | 21815SI <sup>†</sup> | 15      |
| Caelo    | Dexamethasone acetate | 161066     | 22437SI              | 42      |
| Euro OTC | Dexamethasone acetate | 1708011    | 23693SI              | 24      |

- 146 393 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 100 spectra from 48 *Apo-Ident* customers from 45 batches from the substance/substance group *Dexamethasone acetate*.

| Supplier   | Substance             | Batch       | Spectra |
|------------|-----------------------|-------------|---------|
| Euro OTC   | Dexamethasone acetate | 1110007-02  | 6       |
| Euro OTC   | Dexamethasone acetate | 1110007-01  | 2       |
| Noweda     | Dexamethasone acetate | 1110007-02  | 1       |
| Euro OTC   | Dexamethasone acetate | 1110007-03  | 1       |
| Caelo      | Dexamethasone acetate | 13100408    | 1       |
| Caelo      | Dexamethasone acetate | 13100404    | 3       |
| Caelo      | Dexamethasone acetate | 13100407    | 4       |
| Caelo      | Dexamethasone acetate | 13260701    | 3       |
| Caelo      | Dexamethasone acetate | 13260702    | 1       |
| Caelo      | Dexamethasone acetate | 13260703    | 3       |
| Caelo      | Dexamethasone acetate | 13260705    | 2       |
| Caelo      | Dexamethasone acetate | 1405024-01  | 1       |
| Euro OTC   | Dexamethasone acetate | 1405024-01  | 1       |
| Euro OTC   | Dexamethasone acetate | 1405024-02  | 6       |
| Euro OTC   | Dexamethasone acetate | 140502402   | 1       |
| Euro OTC   | Dexamethasone acetate | 1405024-03  | 9       |
| Caelo      | Dexamethasone acetate | 140502403   | 1       |
| Apomix/AHD | Dexamethasone acetate | 1405024-03  | 1       |
| Euro OTC   | Dexamethasone acetate | 1405024-04  | 3       |
| Caelo      | Dexamethasone acetate | 14200201    | 3       |
| Caelo      | Dexamethasone acetate | 14200205    | 2       |
| Caelo      | Dexamethasone acetate | 14200207    | 1       |
| Caelo      | Dexamethasone acetate | 14200208    | 2       |
| Caelo      | Dexamethasone acetate | 14379607    | 2       |
| Caelo      | Dexamethasone acetate | 14379609    | 1       |
| Caelo      | Dexamethasone acetate | 14379611    | 1       |
| Caelo      | Dexamethasone acetate | 14379616    | 2       |
| Caelo      | Dexamethasone acetate | 15243202    | 2       |
| Caelo      | Dexamethasone acetate | 15243201    | 1       |
| Caelo      | Dexamethasone acetate | 16106604    | 1       |
| Caelo      | Dexamethasone acetate | 16106608    | 1       |
| Caelo      | Dexamethasone acetate |             | 1       |
| Caelo      | Dexamethasone acetate | 11093215    | 1       |
| Caelo      | Dexamethasone acetate | 11093210    | 1       |
| Caelo      | Dexamethasone acetate | 11093211    | 1       |
| Fagron     | Dexamethasone acetate | 1110007-01  | 1       |
| EuRho      | Dexamethasone acetate | 1110007-01  | 1       |
| Caelo      | Dexamethasone acetate | 12021801    | 4       |
| Caelo      | Dexamethasone acetate | 12021803    | 3       |
| VDL        | Dexamethasone acetate | 12021803    | 1       |
| GEHE       | Dexamethasone acetate | 12021805    | 1       |
| Caelo      | Dexamethasone acetate | 12021814    | 2       |
| Caelo      | Dexamethasone acetate | 13100401    | 1       |
| Caelo      | Dexamethasone acetate | 13100403    | 4       |
| Caelo      | Dexamethasone acetate | 13100406    | 1       |
| Noweda     | Dexamethasone acetate | 13100406    | 1       |
| Phönix     | Dexamethasone acetate |             | 1       |
| Caelo      | Dexamethasone acetate | 22/AKD2     | 1       |
| Caelo      | Dexamethasone acetate | 4113I-01326 | 1       |
| Caelo      | Dexamethasone acetate | 3913Q-01326 | 1       |
| Caelo      | Dexamethasone acetate | 5/AD1       | 1       |
| Caelo      | Dexamethasone acetate | 12021811    | 1       |
| euopharma  | Dexamethasone acetate | 1110007-01  | 1       |

- 69 533 spectra from 414 *Apo-Ident* customers from a total of 23 757 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Dexamethasone acetate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Dexamethasone acetate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 220           | 0              | 71 166        |
| Type B | 0              | 336           | 0              | 146 393       |
| Type C | 0              | 99            | 1              | 69 533        |

The substance/substance group *Dexamethasone acetate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.2727 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.2143 %) |
| Type C | 100.0000 % (> 99.8813 %) | 99.0000 % (> 96.0000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21301     | 21301               | 0.00                         | 31.32                           |
| 21593     | 21593               | 0.00                         | 37.34                           |
| 21614     | 21301               | 5.92                         | 36.36                           |
| 21815     | 21593               | 8.76                         | 36.41                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe

mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Dextromethorphan hydrobromide monohydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22318-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Dextromethorphan hydrobromide monohydrate; Dextromethorphan hydrobromidum

### Special notes

When selecting the *Dextromethorphan hydrobromide monohydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Dextromethorphan hydrobromide monohydrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Dextromethorphan... | 15D23-B07-308849 | 22318     | 40      | AR-16-FG-008487-02 |
| Fagron   | Dextromethorphan... | 16A22-B03-321371 | 23103     | 40      | 20160205           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Dextromethorphan - hydrobromide monohydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 132 spectra of 5 reference samples from the substance/substance group *Dextromethorphan hydrobromide monohydrate*.

| Supplier | Substance                         | Batch            | Sample ID          | Spectra |
|----------|-----------------------------------|------------------|--------------------|---------|
| Fagron   | Dextromethorphan hydrobromid. ... | 15D23-B07-308849 | 22318 <sup>†</sup> | 20      |
| Fagron   | Dextromethorphan hydrobromid. ... | 15D23-B07-308849 | 22326              | 60      |
| Fagron   | Dextromethorphan hydrobromid. ... | 16E23-B02-329706 | 23593              | 40      |
| Fagron   | Dextromethorphan hydrobromid. ... | 14H27-B04-299502 | not required       | 7       |
| Fagron   | Dextromethorphan hydrobromid. ... | 16A22-B03-321371 | not required       | 5       |

- 146 597 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Dextromethorphan hydrobromide monohydrate*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier | Substance                         | Batch            | Spectra |
|----------|-----------------------------------|------------------|---------|
| Fagron   | Dextromethorphan hydrobromid. . . | 16A22-B03-319331 | 1       |

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Dextromethorphan hydrobromide monohydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Dextromethorphan hydrobromide monohydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 132           | 0              | 146 597       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Dextromethorphan hydrobromide monohydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.4545 %) |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22318     | 22318               | 0.00                         | 44.86                           |
| 23103     | 22318               | 3.23                         | 45.37                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **D-galactose**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20326-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

D-galactose; D-Galactopyranose; Galactosum

### Special notes

When selecting the *D-galactose* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *D-galactose*:

| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate        |
|----------|-------------|------------------|-----------|---------|--------------------|
| Hirundo  | D-galactose | 6878838-1209     | 20841     | 40      | 1401136            |
| Falcento | D-galactose | 007223PF3        | 20894     | 40      | 20130128           |
| Fagron   | D-galactose | 13I13-B40-287993 | 21762     | 40      | AR-15-FG-008936-01 |
| Fagron   | D-galactose | 14H05-B09-310972 | 22259     | 40      | 20140818           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *D-galactose*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 230 spectra of 7 reference samples from the substance/substance group *D-galactose*.

| Supplier           | Substance   | Batch            | Sample ID          | Spectra |
|--------------------|-------------|------------------|--------------------|---------|
| inalc              | D-galactose | 372PF1           | 20259              | 30      |
| Kaden Biochemicals | D-galactose | 13               | 20326              | 40      |
| Fagron             | D-galactose | 11F30-N08        | 20839              | 40      |
| Fagron             | D-galactose | 13I13-B40-287993 | 21762 <sup>†</sup> | 20      |
| Fagron             | D-galactose | 14H05-B09-310972 | 22259 <sup>†</sup> | 20      |
| Fagron             | D-galactose | 15G13-B04-320810 | 23106              | 40      |
| Fagron             | D-galactose | 15G13-B04-320810 | 23595              | 40      |

- 146 499 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 30 spectra from 5 *Apo-Ident* customers from 21 batches from the substance/substance group *D-galactose*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier          | Substance   | Batch            | Spectra |
|-------------------|-------------|------------------|---------|
| Phönix            | D-galactose | 12223PF4         | 2       |
| inalco            | D-galactose | 212619PF5        | 1       |
| Falcento          | D-galactose | 1223PF4          | 3       |
| Falcento          | D-galactose | 122PF4           | 1       |
| Falcento          | D-galactose | 2223PF4          | 3       |
| Falcento          | D-galactose | 222PF4           | 1       |
| Falcento          | D-galactose | 5223PF4          | 3       |
| Phönix            | D-galactose | 39223PF3         | 2       |
| Falcento          | D-galactose | 2014             | 1       |
| Falcento          | D-galactose | 13223PF4         | 1       |
| Falcento          | D-galactose | 48223PF2         | 1       |
| Falcento          | D-galactose | 10440003         | 1       |
| Denk              | D-galactose | 10440003         | 1       |
| Phönix 04.03.2014 | D-galactose |                  | 1       |
| falcento          | D-galactose | 322619PF5        | 1       |
| Fagron            | D-galactose | 16G22-B01-329906 | 1       |
| Fagron            | D-galactose | 10E06-N01        | 1       |
| Fagron            | D-galactose | 11L19-N07        | 1       |
| Fagron            | D-galactose | 12B09-N02        | 1       |
| Ruth              | D-galactose | 142185443        | 1       |
| Denk              | D-galactose |                  | 1       |
| AppliChem         | D-galactose | 2K003859         | 1       |

- 69 603 spectra from 414 *Apo-Ident* customers from a total of 23 781 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *D-galactose* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *D-galactose* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 182           | 48             | 146 499       |
| <b>Type C</b> | 0              | 30            | 0              | 69 603        |

The substance/substance group *D-galactose* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 79.1304 % (> 77.8261 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 80.0000 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20841     | 20841               | 0.00                         | 51.34                           |
| 20894     | 21762               | 11.62                        | 49.13                           |
| 21762     | 21762               | 0.00                         | 48.02                           |
| 22259     | 21762               | 4.88                         | 48.75                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Diclofenac sodium**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20022-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Diclofenac sodium; Diclofenacum natricum; Natrii diclofenaci

### Special notes

When selecting the *Diclofenac sodium* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Diclofenac sodium*:

| Supplier | Substance         | Batch     | Sample ID | Spectra | Certificate |
|----------|-------------------|-----------|-----------|---------|-------------|
| Caelo    | Diclofenac sodium | 12214219  | 20883     | 29      | 20120815    |
| Fagron   | Diclofenac sodium | 13E03-N02 | 20886     | 40      | 20130515    |
| Fagron   | Diclofenac sodium | 12L28-B05 | 21261     | 40      | 20130123    |
| Caelo    | Diclofenac sodium | 13214311  | 21467     | 40      | 20130826    |
| Caelo    | Diclofenac sodium | 13214311  | 21470     | 40      | 20130826    |
| Euro OTC | Diclofenac sodium | 1607016   | 22694     | 40      | 20160808*   |
| Caelo    | Diclofenac sodium | 163492    | 23037     | 40      | 20170112*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 269 spectra of 7 reference samples from the substance/substance group *Diclofenac sodium*. These samples are listed above in the [calibration samples](#) section.
- 71 117 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 170 spectra of 5 reference samples from the substance/substance group *Diclofenac sodium*.

| Supplier | Substance         | Batch            | Sample ID          | Spectra |
|----------|-------------------|------------------|--------------------|---------|
| Caelo    | Diclofenac sodium | 80110508         | 20022              | 30      |
| Euro OTC | Diclofenac sodium | 1403013-01       | 21330              | 40      |
| Caelo    | Diclofenac sodium | 13214311         | 21467 <sup>†</sup> | 20      |
| Caelo    | Diclofenac sodium | 13214311         | 21470 <sup>†</sup> | 20      |
| Fagron   | Diclofenac sodium | 15D14-B04-307452 | 21979              | 60      |

- 146 559 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 146 spectra from 70 *Apo-Ident* customers from 59 batches from the substance/substance group *Diclofenac sodium*.

| Supplier       | Substance         | Batch            | Spectra |
|----------------|-------------------|------------------|---------|
| Fagron         | Diclofenac sodium | 5041401          | 1       |
| Caelo          | Diclofenac sodium | 5081501          | 1       |
| Fagron         | Diclofenac sodium | 10031505         | 1       |
| Euro OTC       | Diclofenac sodium | 11091404         | 1       |
| Euro OTC       | Diclofenac sodium | 111104001        | 1       |
| Caelo          | Diclofenac sodium | 12214202         | 1       |
| Euro OTC       | Diclofenac sodium | 12214220         | 1       |
| Caelo          | Diclofenac sodium | 12L28-B05        | 1       |
| Fagron         | Diclofenac sodium | 12L28-B05-289773 | 2       |
| Caelo          | Diclofenac sodium | 13214304         | 1       |
| Caelo          | Diclofenac sodium | 13214308         | 3       |
| Caelo          | Diclofenac sodium | 13214309         | 2       |
| Caelo          | Diclofenac sodium | 13214311         | 8       |
| Fischar/Phönix | Diclofenac sodium | 13214311         | 1       |
| Caelo          | Diclofenac sodium | 13214312         | 2       |
| Caelo          | Diclofenac sodium | 13214316         | 1       |
| Caelo          | Diclofenac sodium | 13214317         | 5       |
| Caelo          | Diclofenac sodium | 13214318         | 5       |
| Caelo          | Diclofenac sodium | 13H22-N10        | 1       |
| Euro OTC       | Diclofenac sodium | 1403013-01       | 5       |
| Euro OTC       | Diclofenac sodium | 1403013-02       | 8       |
| EurRho/ Anzag  | Diclofenac sodium | 1403013-03       | 1       |
| Euro OTC       | Diclofenac sodium | 1403013-03       | 3       |
| Phönix         | Diclofenac sodium | 1403013-03       | 1       |
| Fagron         | Diclofenac sodium | 14031411         | 1       |
| Fargron        | Diclofenac sodium | 14G17-B08-297032 | 1       |
| Fagron         | Diclofenac sodium | 14G17-B08-297032 | 5       |
| Caelo          | Diclofenac sodium | 1503014-01       | 1       |
| Euro OTC       | Diclofenac sodium | 1503014-01       | 13      |
| Euro OTC       | Diclofenac sodium | 1503014-02       | 3       |
| Caelo          | Diclofenac sodium | 15169604         | 5       |
| Caelo          | Diclofenac sodium | 15169613         | 1       |
| Caelo          | Diclofenac sodium | 15169616         | 1       |
| Caelo          | Diclofenac sodium | 15169617         | 1       |
| Gehe           | Diclofenac sodium | 15278502         | 1       |
| Fagron         | Diclofenac sodium | 15D14-B04        | 1       |
| AHD            | Diclofenac sodium | 15D14B04314450   | 1       |
| Fagron         | Diclofenac sodium |                  | 1       |
| Fagron         | Diclofenac sodium | 15K23-B03        | 1       |
| Phoenix        | Diclofenac sodium | 15K23-B03        | 1       |
| Fagron         | Diclofenac sodium | 15K23-B03-318519 | 1       |
| Caelo          | Diclofenac sodium | 15K23-B03-318519 | 1       |
| Fagron         | Diclofenac sodium | 15K23-B03-321673 | 2       |
| Fagron         | Diclofenac sodium | 15K23-B03-324025 | 3       |
| Fagron         | Diclofenac sodium | 15K23-B03-327802 | 2       |
| Euro OTC       | Diclofenac sodium | 1607016-01       | 4       |
| Caelo          | Diclofenac sodium | 1607016-01       | 1       |
| Euro OTC       | Diclofenac sodium | 1607016-02       | 1       |
| Euro OTC       | Diclofenac sodium | 25041403         | 1       |
| Fagron         | Diclofenac sodium | RDS/1405/0159A   | 1       |
| Caelo          | Diclofenac sodium | 10335805         | 1       |
| Caelo          | Diclofenac sodium | 11091201         | 1       |
| Euro OTC       | Diclofenac sodium | 1111040-01       | 2       |
| Noweda         | Diclofenac sodium | 11301804         | 1       |
| Noweda         | Diclofenac sodium | 11G12-N06        | 1       |
| Euro OTC       | Diclofenac sodium | 1206026          | 1       |
| Gehe           | Diclofenac sodium | 1206026-01       | 2       |

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| Supplier            | Substance         | Batch      | Spectra |
|---------------------|-------------------|------------|---------|
| Euro OTC            | Diclofenac sodium | 1206026-01 | 6       |
| Sanacorp            | Diclofenac sodium | 1206026-01 | 1       |
| Euro OTC            | Diclofenac sodium | 1206026-02 | 7       |
| Caelo               | Diclofenac sodium | 12214205   | 1       |
| Caelo               | Diclofenac sodium | 12214206   | 1       |
| Caelo               | Diclofenac sodium | 12214219   | 3       |
| Anzag Kassel 270812 | Diclofenac sodium | 12A10-N03  | 1       |
| Fagron              | Diclofenac sodium | 12G02-N07  | 1       |
| Fagron              | Diclofenac sodium | 13E03-N02  | 1       |
| Euro OTC            | Diclofenac sodium | 13111203   | 1       |
| Europharm/Otto      | Diclofenac sodium | 135796     | 1       |
| Caelo               | Diclofenac sodium | 13214303   | 1       |

- 69 487 spectra from 414 *Apo-Ident* customers from a total of 23 742 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Diclofenac sodium* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Diclofenac sodium* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 269           | 0              | 71 117        |
| <b>Type B</b> | 0              | 170           | 0              | 146 559       |
| <b>Type C</b> | 0              | 145           | 1              | 69 487        |

The substance/substance group *Diclofenac sodium* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.7695 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.4706 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 99.3151 % (> 97.2603 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20883     | 23037               | 5.87                         | 59.50                           |
| 20886     | 23037               | 7.07                         | 58.87                           |
| 21261     | 23037               | 6.62                         | 60.32                           |
| 21467     | 23037               | 5.92                         | 57.53                           |
| 21470     | 23037               | 7.99                         | 58.05                           |
| 22694     | 22694               | 0.00                         | 63.13                           |
| 23037     | 23037               | 0.00                         | 57.39                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Diltiazem hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20043-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Diltiazem hydrochloride; Diltiazemi hydrochloridum; Diltiazemum hydrochloricum

### Special notes

When selecting the *Diltiazem hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Diltiazem hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Diltiazem hydroc... | 14C12-B04        | 21270     | 40      | 20140417    |
| Caelo    | Diltiazem hydroc... | 13346914         | 21300     | 40      | 20131028    |
| Caelo    | Diltiazem hydroc... | 161908           | 22631     | 40      | 20160715*   |
| Fagron   | Diltiazem hydroc... | 16G20-B03-328133 | 23016     | 40      | 20160829    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Diltiazem hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 230 spectra of 5 reference samples from the substance/substance group *Diltiazem hydrochloride*.

| Supplier | Substance               | Batch            | Sample ID | Spectra |
|----------|-------------------------|------------------|-----------|---------|
| Caelo    | Diltiazem hydrochloride | 91400279         | 20043     | 30      |
| Caelo    | Diltiazem hydrochloride | 13346914         | 21406     | 60      |
| Caelo    | Diltiazem hydrochloride | 13346914         | 21407     | 60      |
| Fagron   | Diltiazem hydrochloride | 16G20-B03-328133 | 23015     | 40      |
| Caelo    | Diltiazem hydrochloride | 170432           | 23325     | 40      |

- 146 499 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 837 spectra from 250 *Apo-Ident* customers from 209 batches from the substance/substance group *Diltiazem hydrochloride*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier                 | Substance               | Batch            | Spectra |
|--------------------------|-------------------------|------------------|---------|
| Caelo                    | Diltiazem hydrochloride | 10212421         | 1       |
| Caelo                    | Diltiazem hydrochloride | 1091503          | 1       |
| Caelo                    | Diltiazem hydrochloride | 12/AKD12         | 1       |
| Caelo                    | Diltiazem hydrochloride | 12133014         | 2       |
| Caelo                    | Diltiazem hydrochloride | 12133022         | 14      |
| Nachprüfung              | Diltiazem hydrochloride |                  | 1       |
| Fagron                   | Diltiazem hydrochloride | 12D05-N07        | 16      |
| Fagron                   | Diltiazem hydrochloride | 12F19-N10        | 6       |
| Caelo                    | Diltiazem hydrochloride | 13031501         | 1       |
| Phönix                   | Diltiazem hydrochloride | 13196104         | 1       |
| Phönix                   | Diltiazem hydrochloride | 13196106         | 1       |
| 11.08.14 Phoenix         | Diltiazem hydrochloride | 13346901         | 1       |
| Caelo                    | Diltiazem hydrochloride | 13346901         | 9       |
| Phoenix                  | Diltiazem hydrochloride | 13346902         | 1       |
| Caelo                    | Diltiazem hydrochloride | 13346902         | 6       |
| Caelo                    | Diltiazem hydrochloride | 13346903         | 8       |
| Caelo                    | Diltiazem hydrochloride | 13346904         | 9       |
| Caelo                    | Diltiazem hydrochloride | 13346905         | 9       |
| Caelo                    | Diltiazem hydrochloride | 13346914         | 12      |
| Caelo                    | Diltiazem hydrochloride | 13346908         | 4       |
| Fagron                   | Diltiazem hydrochloride | 13346915         | 1       |
| Caelo                    | Diltiazem hydrochloride | 13346915         | 9       |
| Fagron                   | Diltiazem hydrochloride | 1359680007       | 1       |
| Fagron                   | Diltiazem hydrochloride | 135968-0009      | 2       |
| Fagron                   | Diltiazem hydrochloride | 13A02-N05        | 8       |
| Fagron                   | Diltiazem hydrochloride | 13G16-N05        | 23      |
| Caelo                    | Diltiazem hydrochloride | 13G16-N05        | 2       |
| Kuerzel                  | Diltiazem hydrochloride | 13G16-N05        | 1       |
| Fagron                   | Diltiazem hydrochloride | 13J24-B04        | 8       |
| Caelo                    | Diltiazem hydrochloride | 13J24-B04-286569 | 1       |
| Fagron                   | Diltiazem hydrochloride | 13J24-B04-286569 | 8       |
| Fagron                   | Diltiazem hydrochloride | 13J24B04286569   | 3       |
| Fagron                   | Diltiazem hydrochloride | 13J24-B04-286571 | 2       |
| Fagron                   | Diltiazem hydrochloride | 13J24-B04-289432 | 3       |
| Caelo                    | Diltiazem hydrochloride | 1405904          | 1       |
| Caelo                    | Diltiazem hydrochloride | 14059133         | 1       |
| Caelo                    | Diltiazem hydrochloride | 14059502         | 3       |
| Caelo                    | Diltiazem hydrochloride | 14059503         | 2       |
| Caelo                    | Diltiazem hydrochloride | 14059504         | 3       |
| Caelo                    | Diltiazem hydrochloride | 14059513         | 15      |
| Caelo                    | Diltiazem hydrochloride | 14059514         | 14      |
| Berkel AHK               | Diltiazem hydrochloride | 14059514         | 2       |
| phönix                   | Diltiazem hydrochloride | 14059514         | 1       |
| Cealo/Sanacorp           | Diltiazem hydrochloride | 14059514         | 1       |
| Caelo                    | Diltiazem hydrochloride | 140595143        | 1       |
| Caelo                    | Diltiazem hydrochloride | 14059521         | 2       |
| Caelo                    | Diltiazem hydrochloride | 14318402         | 4       |
| Caelo                    | Diltiazem hydrochloride | 14059515         | 1       |
| Caelo                    | Diltiazem hydrochloride | 14318403         | 5       |
| Caelo                    | Diltiazem hydrochloride | 14318409         | 13      |
| Fagron                   | Diltiazem hydrochloride | 14318409         | 1       |
| Caelo                    | Diltiazem hydrochloride | 14318410         | 4       |
| Caelo                    | Diltiazem hydrochloride | 14318412         | 14      |
| phoenix                  | Diltiazem hydrochloride | 14318412         | 1       |
| Caesar&Loretz GmbH/Anzag | Diltiazem hydrochloride | 14318412         | 1       |
| Caelo                    | Diltiazem hydrochloride | 14318413         | 3       |
| Caelo                    | Diltiazem hydrochloride | 14318414         | 3       |
| Caelo                    | Diltiazem hydrochloride | 14318416         | 3       |
| Caelo                    | Diltiazem hydrochloride | 1459513          | 1       |
| Fagron                   | Diltiazem hydrochloride | 14C12B04-294133  | 1       |

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| <b>Supplier</b>            | <b>Substance</b>        | <b>Batch</b>         | <b>Spectra</b> |
|----------------------------|-------------------------|----------------------|----------------|
| Fagron                     | Diltiazem hydrochloride | 14C12-B04            | 11             |
| Fagron                     | Diltiazem hydrochloride | 14C12B04             | 1              |
| Fagron                     | Diltiazem hydrochloride | 14C12-B04-292757     | 17             |
| AHD                        | Diltiazem hydrochloride | 14C12-B04-292757     | 1              |
| Gehe                       | Diltiazem hydrochloride | 14C12-B04-292757     | 1              |
| Sanacorp                   | Diltiazem hydrochloride | 14c12-b04-292757     | 1              |
| Fagron                     | Diltiazem hydrochloride | 14C12-B04-292759     | 4              |
| Fagron                     | Diltiazem hydrochloride | 14c12-b04-292759     | 1              |
| Apomix/Noweda              | Diltiazem hydrochloride | 14C12-B04-292759     | 1              |
| Fagron                     | Diltiazem hydrochloride | 14C12-B04-294133     | 5              |
| Caelo                      | Diltiazem hydrochloride | 14C12-B04-294133     | 1              |
| Fagron                     | Diltiazem hydrochloride | 14C12-B04-294134     | 2              |
| Caelo                      | Diltiazem hydrochloride | 14C12-B04-294135     | 1              |
| Fagron                     | Diltiazem hydrochloride | 14G22-B08            | 6              |
| Fagron                     | Diltiazem hydrochloride | 14G22B08             | 1              |
| Fagron                     | Diltiazem hydrochloride | 14G22-B08-299781     | 9              |
| Fagron                     | Diltiazem hydrochloride | 14G22-B08299781      | 2              |
| Caelo                      | Diltiazem hydrochloride | 14G22-B08-299781     | 1              |
| sittig                     | Diltiazem hydrochloride | 14G22-B08-299781     | 1              |
| Fagron                     | Diltiazem hydrochloride | 14G22-B08-299782     | 3              |
| Fagron                     | Diltiazem hydrochloride | 14G22-B08-299783     | 1              |
| Caelo                      | Diltiazem hydrochloride | 15/246/DI            | 1              |
| Caelo                      | Diltiazem hydrochloride | 15212801             | 9              |
| Caelo                      | Diltiazem hydrochloride | 15212802             | 5              |
| Caelo                      | Diltiazem hydrochloride | 15212806             | 2              |
| Caelo                      | Diltiazem hydrochloride | 1521806              | 1              |
| Caelo                      | Diltiazem hydrochloride | 15230000000000000000 | 1              |
| Caelo                      | Diltiazem hydrochloride | 15230501             | 5              |
| Caelo                      | Diltiazem hydrochloride | 15230502             | 7              |
| Chiesi/Phoenix             | Diltiazem hydrochloride | 15230502             | 1              |
| Caelo                      | Diltiazem hydrochloride | 15230503             | 7              |
| Phönix Gotha               | Diltiazem hydrochloride | 15230503             | 1              |
| Noweda                     | Diltiazem hydrochloride | 15230503             | 1              |
| Caelo                      | Diltiazem hydrochloride | 15230504             | 3              |
| Phoenix                    | Diltiazem hydrochloride | 15230503             | 1              |
| Caelo                      | Diltiazem hydrochloride | 15230507             | 7              |
| Caelo                      | Diltiazem hydrochloride | 15230510             | 1              |
| Caelo                      | Diltiazem hydrochloride | 15230512             | 9              |
| Caelo                      | Diltiazem hydrochloride | 15230513             | 1              |
| Caelo                      | Diltiazem hydrochloride | 15230514             | 2              |
| Caelo                      | Diltiazem hydrochloride | 15414301             | 10             |
| Caelo                      | Diltiazem hydrochloride | 15414302             | 11             |
| Caesar&Loretz GmbH /Anzag  | Diltiazem hydrochloride | 15414302             | 1              |
| Phönix                     | Diltiazem hydrochloride | 15414302             | 1              |
| Caelo                      | Diltiazem hydrochloride | 15414304             | 1              |
| Caelo                      | Diltiazem hydrochloride | 15414305             | 1              |
| Caelo                      | Diltiazem hydrochloride | 15414309             | 3              |
| Jenne                      | Diltiazem hydrochloride | 15414313             | 1              |
| Caelo                      | Diltiazem hydrochloride | 15414313             | 4              |
| Caelo                      | Diltiazem hydrochloride | 15414314             | 2              |
| Gehe                       | Diltiazem hydrochloride | 15414319             | 1              |
| Caesar & Loretz GmbH Hi... | Diltiazem hydrochloride | 15414319             | 1              |
| Caelo                      | Diltiazem hydrochloride | 15414319             | 6              |
| Caelo                      | Diltiazem hydrochloride | 15414321             | 2              |
| Caelo                      | Diltiazem hydrochloride | 15435807             | 1              |
| Fagron                     | Diltiazem hydrochloride | 15B12-B01            | 8              |
| Fagron                     | Diltiazem hydrochloride | 15B12-B01-305399     | 11             |
| Fagron                     | Diltiazem hydrochloride | 15b12-b01-305399     | 2              |
| Fagron                     | Diltiazem hydrochloride | 15B12B01305399       | 1              |
| Caelo                      | Diltiazem hydrochloride | 15B12-B01-305399     | 1              |

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| Supplier        | Substance               | Batch            | Spectra |
|-----------------|-------------------------|------------------|---------|
| Fagron          | Diltiazem hydrochloride | 15B12-B01-305400 | 3       |
| Fagron          | Diltiazem hydrochloride | 15B12B01305400   | 1       |
| Fagron          | Diltiazem hydrochloride | 15B12-B01-305401 | 1       |
| Fagron          | Diltiazem hydrochloride | 15G20-B08        | 2       |
| Fagron          | Diltiazem hydrochloride | 15G20-B08-310792 | 2       |
| Caelo           | Diltiazem hydrochloride | 15G20-B08-312065 | 2       |
| Fagron          | Diltiazem hydrochloride | 15G20-B08-312065 | 4       |
| Fagron          | Diltiazem hydrochloride | 15G20-B08-314375 | 9       |
| Caelo           | Diltiazem hydrochloride | 16190801         | 1       |
| Caesar & Loretz | Diltiazem hydrochloride | 16190806         | 1       |
| Caelo           | Diltiazem hydrochloride | 16190806         | 2       |
| Caelo           | Diltiazem hydrochloride | 16190810         | 3       |
| Caelo           | Diltiazem hydrochloride | 16190807         | 3       |
| Gehe            | Diltiazem hydrochloride | 16190813         | 1       |
| Caelo           | Diltiazem hydrochloride | 16190813         | 3       |
| Caelo           | Diltiazem hydrochloride | 16190814         | 3       |
| Fagron          | Diltiazem hydrochloride | 16A14-B11-322153 | 1       |
| Fagron          | Diltiazem hydrochloride | 16A18-B07        | 7       |
| Fagron          | Diltiazem hydrochloride | 16A18B07316667   | 1       |
| Fagron          | Diltiazem hydrochloride | 16A18-B07-316667 | 5       |
| Fagron          | Diltiazem hydrochloride | 16A18-B07-318732 | 7       |
| Caelo           | Diltiazem hydrochloride | 16A18-B07-318732 | 1       |
| Fagron          | Diltiazem hydrochloride | 16A18-B07-318733 | 1       |
| Fagron          | Diltiazem hydrochloride | 16C14-B11        | 4       |
| Fagron          | Diltiazem hydrochloride | 16C14-B11-320568 | 1       |
| Fagron          | Diltiazem hydrochloride | 16C14B11320849   | 1       |
| Fagron          | Diltiazem hydrochloride | 16C14-B11-320849 | 4       |
| Fagron          | Diltiazem hydrochloride | 16C14-B11-322152 | 1       |
| Fagron          | Diltiazem hydrochloride | 16C14-B11-322642 | 9       |
| Fagron          | Diltiazem hydrochloride | 16C14-B11-322153 | 1       |
| Fagron          | Diltiazem hydrochloride | 16G20-B03        | 3       |
| Hedinger GmbH   | Diltiazem hydrochloride | 16G20-B03        | 1       |
| Fagron          | Diltiazem hydrochloride | 16G20-B03-325903 | 4       |
| Fagron          | Diltiazem hydrochloride | 16G20-B03-328133 | 3       |
| Caelo           | Diltiazem hydrochloride | 16G20-B03-328133 | 1       |
| Fagron          | Diltiazem hydrochloride | 16G20-B03-328253 | 1       |
| Fagron          | Diltiazem hydrochloride | 16L19-B01        | 2       |
| Fagron          | Diltiazem hydrochloride | 16L19-B01-330365 | 3       |
| Caelo           | Diltiazem hydrochloride | 17043203         | 1       |
| Caelo           | Diltiazem hydrochloride | 17043205         | 1       |
| Fagron          | Diltiazem hydrochloride | 17D11-B11-333704 | 2       |
| Sanacorp        | Diltiazem hydrochloride | 17043205         | 1       |
| Caelo           | Diltiazem hydrochloride | 18061511         | 1       |
| Fagron          | Diltiazem hydrochloride | 22082014A        | 1       |
| Caelo           | Diltiazem hydrochloride | 23121402         | 1       |
| Caelo           | Diltiazem hydrochloride | 25041401         | 1       |
| Fagron          | Diltiazem hydrochloride | DIL/M-01314      | 1       |
| Fagron          | Diltiazem hydrochloride | DIL/M-0314       | 1       |
| Fagron          | Diltiazem hydrochloride | DIL/M-10515      | 1       |
| Fagron          | Diltiazem hydrochloride | DIL/M-13114      | 1       |
| Caelo           | Diltiazem hydrochloride | 6031302          | 1       |
| Fagron          | Diltiazem hydrochloride | 612213562        | 1       |
| Fagron          | Diltiazem hydrochloride | 9J14-N17         | 2       |
| Caelo           | Diltiazem hydrochloride | 10069509         | 1       |
| Caelo           | Diltiazem hydrochloride | 10212404         | 3       |
| Caelo           | Diltiazem hydrochloride | 10212411         | 1       |
| Fagron          | Diltiazem hydrochloride | 10808-N01        | 1       |
| Fagron          | Diltiazem hydrochloride | 10D28-N23        | 1       |
| Caelo           | Diltiazem hydrochloride | 10212413         | 1       |
| Fagron          | Diltiazem hydrochloride | 11/01-N08        | 1       |

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| Supplier                   | Substance               | Batch             | Spectra |
|----------------------------|-------------------------|-------------------|---------|
| Fiebig ek:12.27 01.08.12   | Diltiazem hydrochloride | 11/01-N08         | 1       |
| phoenix                    | Diltiazem hydrochloride | 11/01-N08         | 1       |
| Fagron                     | Diltiazem hydrochloride | 11-01-N08         | 1       |
| Caelo                      | Diltiazem hydrochloride | 11091301          | 1       |
| Caelo                      | Diltiazem hydrochloride | 11134103          | 1       |
| Caelo                      | Diltiazem hydrochloride | 11134107          | 1       |
| Caelo                      | Diltiazem hydrochloride | 11134113          | 1       |
| Sanacorp                   | Diltiazem hydrochloride | 11134115          | 4       |
| Caelo                      | Diltiazem hydrochloride | 11134117          | 8       |
| Gehe                       | Diltiazem hydrochloride | 11134117          | 1       |
| Caelo                      | Diltiazem hydrochloride | 11134119          | 1       |
| Sanacorp                   | Diltiazem hydrochloride | 11134121          | 2       |
| Fiebig 10.09.12 ek: 13,... | Diltiazem hydrochloride | 11134119          | 1       |
| Phönix 13.11.12            | Diltiazem hydrochloride | 11A17-N13         | 1       |
| Fagron                     | Diltiazem hydrochloride | 11E18-N04         | 2       |
| Fagron                     | Diltiazem hydrochloride | 11I01-N08         | 2       |
| Sanacorp                   | Diltiazem hydrochloride | 11J28-04511       | 1       |
| Fagron                     | Diltiazem hydrochloride | 11J28-N05         | 3       |
| Fagron                     | Diltiazem hydrochloride | 11I012-N08        | 1       |
| Fagron                     | Diltiazem hydrochloride | 11L20-N06         | 1       |
| Caelo                      | Diltiazem hydrochloride | 11L20-N06         | 1       |
| Fagron                     | Diltiazem hydrochloride | 12/12-N02         | 4       |
| Caelo                      | Diltiazem hydrochloride | 12/12-N02         | 1       |
| Gehe                       | Diltiazem hydrochloride | 12/12-N02         | 1       |
| Piramal Healthcare Ltd...  | Diltiazem hydrochloride | 12/12-N02         | 1       |
| Sanacorp                   | Diltiazem hydrochloride | 12/12-N02         | 2       |
| Caelo                      | Diltiazem hydrochloride | 12133006          | 1       |
| Caelo                      | Diltiazem hydrochloride | 12133008          | 2       |
| Alliance                   | Diltiazem hydrochloride | 12133008          | 1       |
| Caelo                      | Diltiazem hydrochloride | 12133009          | 7       |
| Gehe                       | Diltiazem hydrochloride | 12133009          | 1       |
| Alliance                   | Diltiazem hydrochloride | 12133009          | 1       |
| Caelo                      | Diltiazem hydrochloride | 12133010          | 16      |
| Kehr                       | Diltiazem hydrochloride | 12133010          | 1       |
| Noweda                     | Diltiazem hydrochloride | 12133010          | 1       |
| Caesar & Loretz GmbH       | Diltiazem hydrochloride | 12133010          | 1       |
| Sanacorp                   | Diltiazem hydrochloride | 12133010          | 1       |
| Gehe                       | Diltiazem hydrochloride | 12133010          | 1       |
| Caelo                      | Diltiazem hydrochloride | 12133011          | 4       |
| Noweda                     | Diltiazem hydrochloride | 12133022          | 1       |
| Gehe                       | Diltiazem hydrochloride | 12133022          | 1       |
| Caelo                      | Diltiazem hydrochloride | 12133023          | 2       |
| Caelo                      | Diltiazem hydrochloride | 12133028          | 4       |
| Caelo                      | Diltiazem hydrochloride | 12133029          | 3       |
| Noweda                     | Diltiazem hydrochloride | 12133029          | 1       |
| Caelo                      | Diltiazem hydrochloride | 12133032          | 1       |
| Caelo                      | Diltiazem hydrochloride | 12176801          | 2       |
| Noweda                     | Diltiazem hydrochloride | 12176801          | 1       |
| Anzag, 03.11.2012          | Diltiazem hydrochloride | 12176801          | 1       |
| Phönix                     | Diltiazem hydrochloride | 12176801          | 1       |
| Caelo                      | Diltiazem hydrochloride | 12176804          | 1       |
| Caelo                      | Diltiazem hydrochloride | 12177101          | 14      |
| Fagron                     | Diltiazem hydrochloride | 12d05-n07         | 2       |
| Fagron                     | Diltiazem hydrochloride | 12D05-n07         | 1       |
| Noweda                     | Diltiazem hydrochloride | 12D05-N07         | 1       |
| Phönix, 28.03.2013         | Diltiazem hydrochloride | 12D05-N07         | 1       |
| Fagron                     | Diltiazem hydrochloride | 12D05-N070        | 1       |
| Fagron                     | Diltiazem hydrochloride | 12F19-N100102/574 | 1       |
| Piramal Healthcare LTD.    | Diltiazem hydrochloride | 12F19-N10         | 1       |
| Gehe                       | Diltiazem hydrochloride | 12F19-N10         | 1       |

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| Supplier                   | Substance               | Batch            | Spectra |
|----------------------------|-------------------------|------------------|---------|
| Fagron                     | Diltiazem hydrochloride | 12I12-N02        | 2       |
| Alliance Healthcare        | Diltiazem hydrochloride | 12I12-N02        | 1       |
| Fagron                     | Diltiazem hydrochloride | 12K07-N02        | 2       |
| Fagron                     | Diltiazem hydrochloride | 12I12-N02        | 1       |
| Caelo                      | Diltiazem hydrochloride | 13I9604          | 1       |
| Caelo                      | Diltiazem hydrochloride | 13I96103         | 4       |
| Caelo                      | Diltiazem hydrochloride | 13I96104         | 10      |
| Caelo                      | Diltiazem hydrochloride | 13I96105         | 20      |
| Caelo                      | Diltiazem hydrochloride | 13I96107         | 3       |
| Caelo                      | Diltiazem hydrochloride | 1334609          | 1       |
| Noweda                     | Diltiazem hydrochloride | 13346901         | 1       |
| Phoenix                    | Diltiazem hydrochloride | 13346914         | 1       |
| Alliance Health            | Diltiazem hydrochloride | 13A02-N05        | 1       |
| Fagron                     | Diltiazem hydrochloride | 13a02-n05        | 1       |
| Fagron                     | Diltiazem hydrochloride | 13A02N05         | 3       |
| AHD, 26.08.13              | Diltiazem hydrochloride | 13A02-N05        | 1       |
| Caelo                      | Diltiazem hydrochloride | 13A02-N05        | 2       |
| Fagron                     | Diltiazem hydrochloride | 13F13-N05        | 11      |
| Phönix                     | Diltiazem hydrochloride | 13F13-N05        | 1       |
| Bombastus                  | Diltiazem hydrochloride | 13F13-N05        | 1       |
| Fagron                     | Diltiazem hydrochloride | 13G16-N005       | 1       |
| Caelo                      | Diltiazem hydrochloride | 13G16-No5        | 1       |
| Sanacorp                   | Diltiazem hydrochloride | 13j24-b04-286569 | 1       |
| Fagron                     | Diltiazem hydrochloride | 13J24-B04-286570 | 1       |
| Caelo                      | Diltiazem hydrochloride | 13j24-b04-286571 | 1       |
| Fagron                     | Diltiazem hydrochloride | 15B12-B01-305299 | 1       |
| Caelo                      | Diltiazem hydrochloride | 15B12-B01-305400 | 1       |
| Caelo                      | Diltiazem hydrochloride | 23I0213562       | 1       |
| Caelo                      | Diltiazem hydrochloride | 20I60812-1       | 1       |
| Caelo                      | Diltiazem hydrochloride | 2704213562       | 1       |
| Caelo                      | Diltiazem hydrochloride | 33I3U-03562      | 1       |
| Fagron                     | Diltiazem hydrochloride | 37I3M-03562      | 1       |
| Caelo                      | Diltiazem hydrochloride | DIL/M-04511      | 1       |
| Caelo                      | Diltiazem hydrochloride |                  | 1       |
| Caelo                      | Diltiazem hydrochloride | DIL/M-19911      | 1       |
| Herbasinica                | Diltiazem hydrochloride |                  | 1       |
| Caelo                      | Diltiazem hydrochloride | 13I96106         | 3       |
| VDL;18.02.15;15,95EUR      | Diltiazem hydrochloride | 14059514         | 1       |
| Fagron                     | Diltiazem hydrochloride | 15b12-b01-305400 | 2       |
| Caelo                      | Diltiazem hydrochloride | 11I34121         | 1       |
| Sanacorp, 18.02.17, 16,... | Diltiazem hydrochloride | 16I90807         | 1       |
| Caelo                      | Diltiazem hydrochloride | 1233011          | 1       |
| Caelo                      | Diltiazem hydrochloride | 12D05-N07        | 1       |
| Fagron                     | Diltiazem hydrochloride | 14c12-b04-294134 | 1       |
| Fagron                     | Diltiazem hydrochloride | 14C12-B04-294135 | 1       |
| Caelo                      | Diltiazem hydrochloride | 11I34101         | 1       |
| Caelo                      | Diltiazem hydrochloride | 11I34115         | 1       |
| Fagron                     | Diltiazem hydrochloride | 12/12-N02        | 1       |
| Sanacorp                   | Diltiazem hydrochloride | 12I12-N02        | 1       |
| Caelo                      | Diltiazem hydrochloride | 1396103          | 1       |

- 68 796 spectra from 414 *Apo-Ident* customers from a total of 23 595 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Diltiazem hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Diltiazem hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 160           | 0              | 71 226        |
| Type B | 0              | 230           | 0              | 146 499       |
| Type C | 0              | 813           | 24             | 68 796        |

The substance/substance group *Diltiazem hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.3913 %) |
| Type C | 100.0000 % (> 99.8812 %) | 97.1326 % (> 96.7742 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21270     | 22631               | 13.45                        | 48.71                           |
| 21300     | 22631               | 11.15                        | 39.56                           |
| 22631     | 22631               | 0.00                         | 48.35                           |
| 23016     | 22631               | 17.33                        | 49.65                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Dimethyl fumarate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21558-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Dimethyl fumarate

### Special notes

When selecting the *Dimethyl fumarate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Dimethyl fumarate*:

| Supplier | Substance         | Batch      | Sample ID | Spectra | Certificate |
|----------|-------------------|------------|-----------|---------|-------------|
| Caelo    | Dimethyl fumarate | 13269801   | 21558     | 40      | 1506634     |
| Euro OTC | Dimethyl fumarate | 1410013-01 | 21833     | 40      | 20141125    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Dimethyl fumarate*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 40 spectra of 2 reference samples from the substance/substance group *Dimethyl fumarate*.

| Supplier | Substance         | Batch      | Sample ID          | Spectra |
|----------|-------------------|------------|--------------------|---------|
| Caelo    | Dimethyl fumarate | 13269801   | 21558 <sup>†</sup> | 20      |
| Euro OTC | Dimethyl fumarate | 1410013-01 | 21833 <sup>†</sup> | 20      |

- 146 689 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Dimethyl fumarate*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



## Validation results

The validation runs checked whether the substance/substance group *Dimethyl fumarate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Dimethyl fumarate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 40            | 0              | 146 689       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Dimethyl fumarate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 85.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21558     | 21558               | 0.00                         | 62.13                           |
| 21833     | 21558               | 5.29                         | 60.47                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Diphenhydramine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20186-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Diphenhydramine hydrochloride; Diphenhydramini hydrochloridum; Diphenhydraminum hydrochloricum

### Special notes

When selecting the *Diphenhydramine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Diphenhydramine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Caelo    | Diphenhydramine ... | 12329816         | 21464     | 30      | 20121119           |
| Caelo    | Diphenhydramine ... | 16004901         | 23235     | 40      | 20160122           |
| Fagron   | Diphenhydramine ... | 16C25-B03-331026 | 23262     | 40      | AR-17-FG-015432-02 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 110 spectra of 3 reference samples from the substance/substance group *Diphenhydramine - hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 276 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 5 reference samples from the substance/substance group *Diphenhydramine - hydrochloride*.

| Supplier | Substance                     | Batch    | Sample ID          | Spectra |
|----------|-------------------------------|----------|--------------------|---------|
| Caelo    | Diphenhydramine hydrochloride | 82811299 | 20186              | 50      |
| Caelo    | Diphenhydramine hydrochloride | 82811179 | 20321              | 40      |
| Caelo    | Diphenhydramine hydrochloride | 12329816 | 21304              | 40      |
| Caelo    | Diphenhydramine hydrochloride | 12329816 | 21464 <sup>†</sup> | 30      |
| Caelo    | Diphenhydramine hydrochloride | 15072617 | 23206              | 40      |

- 146 529 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 59 spectra from 33 *Apo-Ident* customers from 39 batches from the substance/substance group *Diphenhydramine hydrochloride*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier            | Substance                     | Batch            | Spectra |
|---------------------|-------------------------------|------------------|---------|
| Caelo               | Diphenhydramine hydrochloride | 2041403          | 1       |
| PHOENIX 29.01.2013  | Diphenhydramine hydrochloride | 120208           | 1       |
| Caelo               | Diphenhydramine hydrochloride | 12329815         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 12329816         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 13100462         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 13331810         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 13331813         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 13343104         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 15072602         | 3       |
| Caelo               | Diphenhydramine hydrochloride | 15072603         | 2       |
| Caelo               | Diphenhydramine hydrochloride | 15072608         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 15072609         | 2       |
| Caelo               | Diphenhydramine hydrochloride | 15072614         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 15220402         | 1       |
| Noweda              | Diphenhydramine hydrochloride | 15220402         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 15220403         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 15220404         | 3       |
| Caelo               | Diphenhydramine hydrochloride | 15220405         | 2       |
| Fagron              | Diphenhydramine hydrochloride | 16C25-B03-331026 | 1       |
| Caelo               | Diphenhydramine hydrochloride | 1814A-01339      | 1       |
| Caelo               | Diphenhydramine hydrochloride | 1912I-01339      | 1       |
| Caelo               | Diphenhydramine hydrochloride | 20071502         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 2215I-01339      | 1       |
| Caelo               | Diphenhydramine hydrochloride | 31031508         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 4061205          | 1       |
| Caelo               | Diphenhydramine hydrochloride | 5121204          | 1       |
| Finze               | Diphenhydramine hydrochloride | 9F05-N04         | 3       |
| Caelo               | Diphenhydramine hydrochloride | 10122030         | 4       |
| Caelo               | Diphenhydramine hydrochloride | 12007702         | 1       |
| Caesar/Noweda       | Diphenhydramine hydrochloride | 12007714         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 12007715         | 2       |
| Caelo               | Diphenhydramine hydrochloride | 12007716         | 1       |
| Noweda              | Diphenhydramine hydrochloride | 12007716         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 12007720         | 1       |
| Caelo               | Diphenhydramine hydrochloride | 12007721         | 3       |
| Sanacorp            | Diphenhydramine hydrochloride | 12329805         | 1       |
| Phoenix, 18.09.2012 | Diphenhydramine hydrochloride | 12F28-N01        | 1       |
| Anzag 16.03.2013    | Diphenhydramine hydrochloride | 12J04-N02        | 1       |
| Fagron              | Diphenhydramine hydrochloride | 12F28-N01        | 1       |
| Fagron              | Diphenhydramine hydrochloride | 12J04-N02        | 2       |
| Fagron              | Diphenhydramine hydrochloride | 12L17-N03        | 1       |
| Fagron              | Diphenhydramine hydrochloride | 13A14-B40        | 1       |
| Caelo               | Diphenhydramine hydrochloride | 25071306         | 1       |

- 69 574 spectra from 414 *Apo-Ident* customers from a total of 23 763 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Diphenhydramine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Diphenhydramine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or

incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 110           | 0              | 71 276        |
| <b>Type B</b> | 0              | 199           | 1              | 146 529       |
| <b>Type C</b> | 0              | 42            | 17             | 69 574        |

The substance/substance group *Diphenhydramine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.5455 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.5000 % (> 98.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 71.1864 % (> 66.1017 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21464     | 23262               | 20.65                        | 44.75                           |
| 23235     | 23262               | 11.00                        | 44.97                           |
| 23262     | 23262               | 0.00                         | 46.63                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Diphenylcyclopropenone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20934-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Diphenylcyclopropenone; Diphenylcyclopropenonum

### Special notes

When selecting the *Diphenylcyclopropenone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Diphenylcyclopropenone*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Diphenylcyclopro... | 12L17-N07        | 20934     | 40      | 1407599     |
| Fagron   | Diphenylcyclopro... | 15J12-B01-316620 | 22362     | 40      | 9341        |
| Fagron   | Diphenylcyclopro... | 16F02-B10-329708 | 23070     | 40      | 20160822    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Diphenylcyclopropanone*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 137 spectra of 5 reference samples from the substance/substance group *Diphenylcyclopropanone*.

| Supplier | Substance              | Batch            | Sample ID          | Spectra |
|----------|------------------------|------------------|--------------------|---------|
| Fagron   | Diphenylcyclopropanone | 13I26-N12        | 21342              | 40      |
| Fagron   | Diphenylcyclopropanone | 13I26-N12        | 21539              | 35      |
| Fagron   | Diphenylcyclopropanone | 15J12-B01-316620 | 22362 <sup>†</sup> | 20      |
| Fagron   | Diphenylcyclopropanone | 16F02-B10-326265 | 23071              | 40      |
| Fagron   | Diphenylcyclopropanone | 16F02-B10-327812 | not required       | 2       |

- 146 592 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Diphenylcyclopropanone*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are docu-

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

mented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Diphenylcyclopropenone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Diphenylcyclopropenone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 22            | 115            | 146 592       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Diphenylcyclopropenone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 16.0584 % (> 13.8686 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20934     | 20934               | 0.00                         | 30.41                           |
| 22362     | 22362               | 0.00                         | 25.05                           |
| 23070     | 22362               | 12.03                        | 27.54                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Doxycycline hyclate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20796-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Doxycycline hyclate; Doxycyclini hyclas; Doxycyclinum hemiaethanolicum hemihydricum

### Special notes

When selecting the *Doxycycline hyclate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Doxycycline hyclate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Doxycycline hycl... | 12G12-N15        | 20796     | 40      | 1404233     |
| Fagron   | Doxycycline hycl... | 12G12-N15        | 20821     | 40      | 20120807    |
| Fagron   | Doxycycline hycl... | 14K28-B05-312218 | 22242     | 40      | 20150216    |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Doxycycline hyclate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *Doxycycline hyclate*.

| Supplier | Substance           | Batch            | Sample ID          | Spectra |
|----------|---------------------|------------------|--------------------|---------|
| Fagron   | Doxycycline hyclate | 14K28-B05-312218 | 22242 <sup>†</sup> | 20      |
| Fagron   | Doxycycline hyclate | 16I06-B02-330167 | 23118              | 40      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 4 spectra from 3 *Apo-Ident* customers from 4 batches from the substance/substance group *Doxycycline hyclate*.

| Supplier                   | Substance           | Batch            | Spectra |
|----------------------------|---------------------|------------------|---------|
| Löwen City-Apotheke Bar... | Doxycycline hyclate | 2042015          | 1       |
| Fagron                     | Doxycycline hyclate | 12G12-N15        | 1       |
| Fagron                     | Doxycycline hyclate | 13D24-B40-298948 | 1       |
| Löwen City-Apotheke Bar... | Doxycycline hyclate | 10022014         | 1       |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Doxycycline hyclate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Doxycycline hyclate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 4             | 0              | 69 629        |

The substance/substance group *Doxycycline hyclate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20796     | 20796               | 0.00                         | 32.07                           |
| 20821     | 20796               | 1.86                         | 31.65                           |
| 22242     | 20796               | 10.70                        | 32.52                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe

mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Doxylamine hydrogen succinate</b>                            |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20315-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Doxylamine hydrogen succinate; Doxylamini hydrogenosuccinas; Doxylaminum succinicum

### Special notes

When selecting the *Doxylamine hydrogen succinate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Doxylamine hydrogen succinate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Doxylamine hydro... | 14F03-B01-293498 | 21542     | 40      | 1410524            |
| Fagron   | Doxylamine hydro... | 15F01-B04-309189 | 22601     | 40      | AR-16-FG-011361-01 |
| Caelo    | Doxylamine hydro... | 15203906         | 23085     | 40      | 20151112           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Doxylamine hydrogen succinate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Doxylamine hydrogen succinate*.

| Supplier | Substance                     | Batch            | Sample ID          | Spectra |
|----------|-------------------------------|------------------|--------------------|---------|
| Fagron   | Doxylamine hydrogen succinate | 700296           | 20315              | 40      |
| Fagron   | Doxylamine hydrogen succinate | 14F03-B01-293498 | 21542 <sup>†</sup> | 20      |
| Caelo    | Doxylamine hydrogen succinate | 15203906         | 23086              | 40      |
| Caelo    | Doxylamine hydrogen succinate | 172047           | 23626              | 40      |

- 146 589 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 37 spectra from 11 *Apo-Ident* customers from 16 batches from the substance/substance group *Doxylamine hydrogen succinate*.

| Supplier | Substance                     | Batch     | Spectra |
|----------|-------------------------------|-----------|---------|
| Fagron   | Doxylamine hydrogen succinate | 12E29-N03 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

continued from previous page

| Supplier                   | Substance                     | Batch            | Spectra |
|----------------------------|-------------------------------|------------------|---------|
| Fagron                     | Doxylamine hydrogen succinate | 14K27-B07        | 1       |
| Fagron                     | Doxylamine hydrogen succinate | 14F03-B01-296846 | 1       |
| Fagron                     | Doxylamine hydrogen succinate | 12E04-N04        | 4       |
| Fagron                     | Doxylamine hydrogen succinate | 15K04-B01        | 1       |
| Fagron                     | Doxylamine hydrogen succinate | 12G10-N03        | 6       |
| Caesar & Loretz GmbH, 4... | Doxylamine hydrogen succinate | 13A04-N02        | 4       |
| Fagron                     | Doxylamine hydrogen succinate | 13A04-N02        | 3       |
| Fagron                     | Doxylamine hydrogen succinate | 13E29-N03        | 4       |
| Fagron                     | Doxylamine hydrogen succinate | 14F03B01293498   | 1       |
| Fagron                     | Doxylamine hydrogen succinate | 15K04B01321379   | 1       |
| Fagron                     | Doxylamine hydrogen succinate | 13/26-N14        | 1       |
| Fagron                     | Doxylamine hydrogen succinate | 483875887        | 1       |
| Fagron                     | Doxylamine hydrogen succinate | 11G20-N10        | 1       |
| Fagron                     | Doxylamine hydrogen succinate | 11K17-N04        | 3       |
| Fagron                     | Doxylamine hydrogen succinate | 12K21-N01        | 3       |
| Fagron                     | Doxylamine hydrogen succinate | 12811328003      | 1       |

- 69 596 spectra from 414 *Apo-Ident* customers from a total of 23 786 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Doxylamine hydrogen succinate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Doxylamine hydrogen succinate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 140           | 0              | 146 589       |
| <b>Type C</b> | 0              | 33            | 4              | 69 596        |

The substance/substance group *Doxylamine hydrogen succinate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.7143 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 89.1892 % (> 81.0811 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21542     | 21542               | 0.00                         | 26.59                           |
| 22601     | 22601               | 0.00                         | 29.58                           |
| 23085     | 22601               | 9.34                         | 32.01                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Drofenine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20320-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Drofenine hydrochloride; Drofenini hydrochloridum; Drofeninum hydrochloricum

### Special notes

When selecting the *Drofenine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Drofenine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Drofenine hydroc... | 13I09-N05        | 21275     | 40      | 20130524           |
| Fagron   | Drofenine hydroc... | 15G01-B04-330979 | 23233     | 40      | AR-17-FG-015434-02 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Drofenine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 3 reference samples from the substance/substance group *Drofenine hydrochloride*.

| Supplier | Substance               | Batch            | Sample ID | Spectra |
|----------|-------------------------|------------------|-----------|---------|
| Fagron   | Drofenine hydrochloride | 10K29            | 20320     | 40      |
| Fagron   | Drofenine hydrochloride | 15G01-B04-323028 | 22807     | 40      |
| Fagron   | Drofenine hydrochloride | 15G01-B04-330979 | 23412     | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 2 spectra from 1 *Apo-Ident* customers from 2 batches from the substance/substance group *Drofenine hydrochloride*.

| Supplier | Substance               | Batch     | Spectra |
|----------|-------------------------|-----------|---------|
| Fagron   | Drofenine hydrochloride | 11J24-N01 | 1       |
| Fagron   | Drofenine hydrochloride | 12D04-N03 | 1       |

- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Drofenine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Drofenine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 120           | 0              | 146 609       |
| <b>Type C</b> | 0              | 2             | 0              | 69 631        |

The substance/substance group *Drofenine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21275     | 23233               | 7.88                         | 49.67                           |
| 23233     | 23233               | 0.00                         | 50.87                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe

von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Econazole nitrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20849-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Econazole nitrate; Econazoli nitras; Econazolum nitricum

### Special notes

When selecting the *Econazole nitrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Econazole nitrate*:

| Supplier | Substance         | Batch            | Sample ID | Spectra | Certificate        |
|----------|-------------------|------------------|-----------|---------|--------------------|
| Fagron   | Econazole nitrate | 12H08-N02        | 20849     | 40      | 1312442            |
| Fagron   | Econazole nitrate | 11F09-N16        | 21268     | 40      | 20110606           |
| Fagron   | Econazole nitrate | 12I06-B40-306925 | 22392     | 40      | AR-16-FG-011359-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Econazole nitrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *Econazole nitrate*.

| Supplier | Substance         | Batch            | Sample ID | Spectra |
|----------|-------------------|------------------|-----------|---------|
| Fagron   | Econazole nitrate | 14G22-B07-327805 | 23079     | 40      |
| Fagron   | Econazole nitrate | 12I06-B40-306925 | 22392SI   | 40      |

- 146 649 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 3 spectra from 2 *Apo-Ident* customers from 2 batches from the substance/substance group *Econazole nitrate*.

| Supplier | Substance         | Batch            | Spectra |
|----------|-------------------|------------------|---------|
| Fagron   | Econazole nitrate | 12I06-B40-289953 | 2       |
| Fagron   | Econazole nitrate | 13D22-N06        | 1       |

- 69 630 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Econazole nitrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Econazole nitrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 2             | 1              | 69 630        |

The substance/substance group *Econazole nitrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8817 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20849     | 20849               | 0.00                         | 31.51                           |
| 21268     | 22392               | 8.21                         | 35.62                           |
| 22392     | 22392               | 0.00                         | 31.44                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Eosin yellowish**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20571-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Eosin yellowish; Eosinum natricum

### Special notes

When selecting the *Eosin yellowish* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Eosin yellowish*:

| Supplier | Substance       | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------------|------------------|-----------|---------|-------------|
| Fagron   | Eosin yellowish | 12E25-N01        | 20900     | 55      | pending     |
| Fagron   | Eosin yellowish | 13I11-N03        | 20932     | 40      | 20130925    |
| Fagron   | Eosin yellowish | 13I11-N03        | 21208     | 40      | 20130925    |
| Fagron   | Eosin yellowish | 15G01-T03-025958 | 22261     | 40      | 1604114     |
| Fagron   | Eosin yellowish | 13F14-T01-017395 | 22534     | 40      | 1608469     |
| Fagron   | Eosin yellowish | 13F14-T01-017395 | 22660     | 40      | 1801115     |
| Fagron   | Eosin yellowish | 13F14-T01-017395 | 22816     | 40      | 1705197     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 295 spectra of 7 reference samples from the substance/substance group *Eosin yellowish*. These samples are listed above in the [calibration samples](#) section.
- 71 091 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 105 spectra of 4 reference samples from the substance/substance group *Eosin yellowish*.

| Supplier | Substance       | Batch            | Sample ID          | Spectra |
|----------|-----------------|------------------|--------------------|---------|
| Fagron   | Eosin yellowish | 12A02-N09        | 20571              | 40      |
| Fagron   | Eosin yellowish | 12E25-N01        | 20900 <sup>†</sup> | 5       |
| Fagron   | Eosin yellowish | 15G01-T03-025958 | 22261 <sup>†</sup> | 20      |
| Fagron   | Eosin yellowish | 13F14-T01-017395 | 22535              | 40      |

- 146 624 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 41 spectra from 36 *Apo-Ident* customers from 20 batches from the substance/substance group *Eosin yellowish*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                 | Substance       | Batch             | Spectra |
|--------------------------|-----------------|-------------------|---------|
| Fagron                   | Eosin yellowish | 13/11-N03         | 4       |
| Caelo                    | Eosin yellowish | 13F14-T01-017395  | 1       |
| Fagron                   | Eosin yellowish | 13F14-T01-017395  | 5       |
| Cael Sanacorp 05.02.2016 | Eosin yellowish | 13F14-T01-017395  | 1       |
| Fagron                   | Eosin yellowish | 13fF14-T01-017395 | 1       |
| Caelo                    | Eosin yellowish | 13I11-N03         | 1       |
| Caelo                    | Eosin yellowish | 14H28-M05         | 1       |
| Gehe                     | Eosin yellowish | 14H28-M05         | 1       |
| Fagron                   | Eosin yellowish | 14H28-M05         | 1       |
| Fagron                   | Eosin yellowish | 15G01-T03-025958  | 1       |
| Fargon                   | Eosin yellowish | 14H28-M09         | 1       |
| Fagron                   | Eosin yellowish | 15G01T03025959    | 1       |
| Caelo                    | Eosin yellowish | 15G01-T03-025958  | 1       |
| Fagron                   | Eosin yellowish | EYWS/15/13        | 1       |
| Fagron                   | Eosin yellowish | 11E25-N01         | 1       |
| Fagron                   | Eosin yellowish | 11F21-N10         | 1       |
| Fagron                   | Eosin yellowish | 12A02-N09         | 1       |
| Caelo                    | Eosin yellowish | 12e25-n01         | 1       |
| Sanacorp                 | Eosin yellowish | 12E25-N01         | 1       |
| Fagron                   | Eosin yellowish | 12E25-N01         | 4       |
| Fagron                   | Eosin yellowish | 12H28-N08         | 3       |
| Fargon/Sanacorp          | Eosin yellowish | 13/11-No3         | 1       |
| Fagron                   | Eosin yellowish | 13/11-N03         | 1       |
| Fagron                   | Eosin yellowish | 2512A-01357       | 1       |
| Fagron                   | Eosin yellowish | EYWS/16/11        | 2       |
| Fagron                   | Eosin yellowish | 14H28-M09         | 2       |
| Caelo                    | Eosin yellowish | 12e25n01          | 1       |

- 69 592 spectra from 414 *Apo-Ident* customers from a total of 23 781 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Eosin yellowish* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Eosin yellowish* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 253           | 42             | 71 091        |
| <b>Type B</b> | 0              | 77            | 28             | 146 624       |
| <b>Type C</b> | 0              | 25            | 16             | 69 592        |

The substance/substance group *Eosin yellowish* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate        |
|---------------|--------------------------|-------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 85.7627 % (> 84.7458 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 73.3333 % (> 70.4762 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 60.9756 % (> 53.6585 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20900     | 20900               | 0.00                         | 88.34                           |
| 20932     | 22816               | 11.71                        | 80.20                           |
| 21208     | 22660               | 9.45                         | 78.36                           |
| 22261     | 22261               | 0.00                         | 64.64                           |
| 22534     | 22534               | 0.00                         | 64.60                           |
| 22660     | 22660               | 0.00                         | 86.16                           |
| 22816     | 22816               | 0.00                         | 80.41                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ephedrine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20993-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ephedrine hydrochloride; Ephedrini hydrochloridum; Ephedrinum hydrochloricum

### Special notes

When selecting the *Ephedrine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ephedrine hydrochloride*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Ephedrine hydroc... | 12017217 | 20993     | 40      | 1511635     |
| Caelo    | Ephedrine hydroc... | 13323305 | 21322     | 40      | 20131113    |
| Caelo    | Ephedrine hydroc... | 14378502 | 21803     | 40      | 20150106    |
| Caelo    | Ephedrine hydroc... | 161197   | 22436     | 40      | 20160420*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Ephedrine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 160 spectra of 5 reference samples from the substance/substance group *Ephedrine hydrochloride*.

| Supplier | Substance               | Batch            | Sample ID          | Spectra |
|----------|-------------------------|------------------|--------------------|---------|
| Caelo    | Ephedrine hydrochloride | 10103408         | 20228              | 40      |
| Caelo    | Ephedrine hydrochloride | 14378502         | 21803 <sup>†</sup> | 20      |
| Caelo    | Ephedrine hydrochloride | 161197           | 22436 <sup>†</sup> | 20      |
| Fagron   | Ephedrine hydrochloride | 15H28-B02-316349 | 23073              | 40      |
| Caelo    | Ephedrine hydrochloride | 171736           | 23672              | 40      |

- 146 569 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 44 spectra from 20 *Apo-Ident* customers from 34 batches from the substance/substance group *Ephedrine hydrochloride*.

| Supplier                   | Substance               | Batch        | Spectra |
|----------------------------|-------------------------|--------------|---------|
| GATT-KOLLER/PHOENIX        | Ephedrine hydrochloride | 915/03141314 | 2       |
| Phoenix 04.03.14           | Ephedrine hydrochloride | 1332303      | 1       |
| Caelo                      | Ephedrine hydrochloride | 13323302     | 1       |
| PHOENIX 10.03.2014         | Ephedrine hydrochloride | 13323302     | 1       |
| Gehe am 04.03.14           | Ephedrine hydrochloride | 13323303     | 1       |
| Caelo                      | Ephedrine hydrochloride | 13323305     | 2       |
| Phönix                     | Ephedrine hydrochloride | 13323315     | 1       |
| Caelo                      | Ephedrine hydrochloride | 13323316     | 1       |
| Caelo                      | Ephedrine hydrochloride | 13323309     | 1       |
| Caelo                      | Ephedrine hydrochloride | 13323310     | 1       |
| Fagron                     | Ephedrine hydrochloride | 13L30-B36    | 1       |
| Caelo                      | Ephedrine hydrochloride | 14378502     | 1       |
| Caesar & Loretz GmbH       | Ephedrine hydrochloride | 14378503     | 1       |
| Caelo                      | Ephedrine hydrochloride | 14378506     | 2       |
| Caelo                      | Ephedrine hydrochloride | 14378507     | 1       |
| Caelo                      | Ephedrine hydrochloride | 14378510     | 2       |
| Caelo                      | Ephedrine hydrochloride | 15179302     | 1       |
| Caesar & Loretz GmbH       | Ephedrine hydrochloride | 16119702     | 1       |
| Caelo                      | Ephedrine hydrochloride | 16119703     | 2       |
| Caelo                      | Ephedrine hydrochloride | 16119709     | 1       |
| Caesar & Loretz GmbH, 4... | Ephedrine hydrochloride | 11126411     | 1       |
| Gatt-Koller / Phoenix      | Ephedrine hydrochloride | 18502141114  | 1       |
| Caelo                      | Ephedrine hydrochloride | 11126414     | 1       |
| Caelo                      | Ephedrine hydrochloride | 11126407     | 1       |
| Caelo                      | Ephedrine hydrochloride | 10103425     | 1       |
| Anzag, 24.10.2012          | Ephedrine hydrochloride | 12017205     | 2       |
| Phönix 01.12.12            | Ephedrine hydrochloride | 12017207     | 1       |
| Caelo                      | Ephedrine hydrochloride | 12017215     | 1       |
| Caelo                      | Ephedrine hydrochloride | 12017209     | 2       |
| Caelo                      | Ephedrine hydrochloride | 12017217     | 1       |
| Fagron                     | Ephedrine hydrochloride | 12017220     | 1       |
| Phönix 05.11.2013          | Ephedrine hydrochloride | 12017223     | 1       |
| Caelo                      | Ephedrine hydrochloride | 12017223     | 1       |
| Fagron                     | Ephedrine hydrochloride | 13B19-N04    | 1       |
| Caelo                      | Ephedrine hydrochloride | EphedrinHCL2 | 1       |
| Caelo                      | Ephedrine hydrochloride | EphedrinHCL1 | 1       |
| Caelo                      | Ephedrine hydrochloride | 12017207     | 1       |

- 69 589 spectra from 414 *Apo-Ident* customers from a total of 23 767 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ephedrine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ephedrine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).



|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 160           | 0              | 71 226        |
| Type B | 0              | 160           | 0              | 146 569       |
| Type C | 0              | 44            | 0              | 69 589        |

The substance/substance group *Ephedrine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.2500 %) |
| Type C | 100.0000 % (> 99.8813 %) | 100.0000 % (> 86.3636 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20993     | 20993               | 0.00                         | 40.69                           |
| 21322     | 20993               | 5.18                         | 38.15                           |
| 21803     | 20993               | 1.79                         | 40.35                           |
| 22436     | 22436               | 0.00                         | 45.01                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Epinephrine hydrogen tartrate</b>                            |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20689-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Epinephrine hydrogen tartrate; Adrenalini tartras; Adrenalinum bitartaricum

### Special notes

When selecting the *Epinephrine hydrogen tartrate* substance/substance group, the following information is displayed to the user:

- Advice for the identification of epinephrine bitartrate: According to the BfArM, ephedrine and its salts are considered as critical drugs in compliance to § 5 AMG. Critical drugs must not be placed on the market or be applied to humans.

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Epinephrine hydrogen tartrate*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------------|-----------|-----------|---------|-------------|
| Caelo    | Epinephrine hydr... | 12120202  | 20689     | 40      | 1405614     |
| Fagron   | Epinephrine hydr... | 12L22-N04 | 20749     | 40      | 20120106    |
| Caelo    | Epinephrine hydr... | 12337804  | 21058     | 40      | 20121128    |
| Caelo    | Epinephrine hydr... | 14007802  | 21489     | 40      | 1603180     |
| Caelo    | Epinephrine hydr... | 14007802  | 21489SI   | 40      | 1603180     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Epinephrine hydrogen tartrate*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 775 spectra of 26 reference samples from the substance/substance group *Epinephrine hydrogen tartrate*.

| Supplier | Substance                     | Batch    | Sample ID            | Spectra |
|----------|-------------------------------|----------|----------------------|---------|
| Caelo    | Epinephrine hydrogen tartrate | 12337805 | 21059                | 40      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21489 <sup>†</sup>   | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21490                | 60      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21491                | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21492                | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21493                | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21494                | 60      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21495                | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21496                | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21497                | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21498                | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 162764   | 22777                | 40      |
| Caelo    | Epinephrine hydrogen tartrate | 171115   | 23323                | 40      |
| Caelo    | Epinephrine hydrogen tartrate | 171115   | 23326                | 40      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21489SI <sup>†</sup> | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21490SI              | 60      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21491SI              | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21492SI              | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21493SI              | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21495SI              | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21496SI              | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21497SI              | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 14007802 | 21498SI              | 20      |
| Caelo    | Epinephrine hydrogen tartrate | 162764   | 22777SI              | 40      |
| Caelo    | Epinephrine hydrogen tartrate | 171115   | 23323SI              | 35      |
| Caelo    | Epinephrine hydrogen tartrate | 171115   | 23326SI              | 40      |

- 145 954 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 30 spectra from 17 *Apo-Ident* customers from 25 batches from the substance/substance group *Epinephrine hydrogen tartrate*.

| Supplier                 | Substance                     | Batch             | Spectra |
|--------------------------|-------------------------------|-------------------|---------|
| Fagron                   | Epinephrine hydrogen tartrate | 11L22-N04         | 1       |
| Fagron                   | Epinephrine hydrogen tartrate | 12G11-N07         | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 12120202          | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 12337801          | 2       |
| Alliance Health 12.03.14 | Epinephrine hydrogen tartrate | 12337805          | 1       |
| Phoenix 22.5.14          | Epinephrine hydrogen tartrate | 12337804          | 1       |
| Fagron                   | Epinephrine hydrogen tartrate | 14E12-B02         | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 15239703          | 1       |
| Fagron                   | Epinephrine hydrogen tartrate | 15A13-B02-305559  | 2       |
| Caelo                    | Epinephrine hydrogen tartrate | 162746402         | 1       |
| Fagron                   | Epinephrine hydrogen tartrate | 16E09-B11-319882  | 3       |
| Fagron                   | Epinephrine hydrogen tartrate | 16e09-b11-319882  | 1       |
| Fagron                   | Epinephrine hydrogen tartrate | 12/02-N03         | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 123337805         | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 12337805          | 1       |
| Fagron                   | Epinephrine hydrogen tartrate | 12G11-No70076/130 | 1       |
| Fagron                   | Epinephrine hydrogen tartrate | 13I04-N03         | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 14007808          | 1       |
| Fagron                   | Epinephrine hydrogen tartrate | 13I04-N03         | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 210316-3          | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 15239701          | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 16276402          | 1       |
| AHD 17.11.14 EK 7,60     | Epinephrine hydrogen tartrate |                   | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 10237109          | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 210316-1          | 1       |
| Caelo                    | Epinephrine hydrogen tartrate | 14301002          | 1       |

- 69 603 spectra from 414 *Apo-Ident* customers from a total of 23 776 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

## Validation results

The validation runs checked whether the substance/substance group *Epinephrine hydrogen tartrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Epinephrine hydrogen tartrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 200           | 0              | 71 186        |
| Type B | 0              | 716           | 59             | 145 954       |
| Type C | 0              | 29            | 1              | 69 603        |

The substance/substance group *Epinephrine hydrogen tartrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 92.3871 % (> 92.0000 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 96.6667 % (> 86.6667 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20689     | 20689               | 0.00                         | 50.22                           |
| 20749     | 21489               | 12.12                        | 49.97                           |
| 21058     | 20689               | 6.40                         | 49.76                           |
| 21489     | 21489               | 0.00                         | 50.49                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

IdentModul 1.3-2018-01

Validated substance/substance group **Ergotamine tartrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21341-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

## Relevant substance names

Ergotamine tartrate; Ergotamini tartras; Ergotaminum tartricum

## Special notes

When selecting the *Ergotamine tartrate* substance/substance group, the following information is displayed to the user:

*no information*

## Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

## Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

## Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ergotamine tartrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Ergotamine tartr... | 15B16-B05-308418 | 22361     | 30      | 9384        |
| Fagron   | Ergotamine tartr... | 15B16-B05-308417 | 22722     | 40      | 20150302    |
| Fagron   | Ergotamine tartr... | 15B16-B05-308418 | 22361SI   | 30      | 9384        |
| Fagron   | Ergotamine tartr... | 15B16-B05-308417 | 22722SI   | 40      | 20150302    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 140 spectra of 4 reference samples from the substance/substance group *Ergotamine tartrate*. These samples are listed above in the [calibration samples](#) section.
- 71 246 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 236 spectra of 5 reference samples from the substance/substance group *Ergotamine tartrate*.

| Supplier | Substance           | Batch            | Sample ID            | Spectra |
|----------|---------------------|------------------|----------------------|---------|
| Fagron   | Ergotamine tartrate | 13H02-N01        | 21341                | 100     |
| Fagron   | Ergotamine tartrate | 13I24-B10-288648 | 21540                | 46      |
| Fagron   | Ergotamine tartrate | 13I24-B10-288650 | 21556                | 60      |
| Fagron   | Ergotamine tartrate | 15B16-B05-308418 | 22361 <sup>†</sup>   | 15      |
| Fagron   | Ergotamine tartrate | 15B16-B05-308418 | 22361SI <sup>†</sup> | 15      |

- 146 493 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Ergotamine tartrate*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ergotamine tartrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ergotamine tartrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 140           | 0              | 71 246        |
| <b>Type B</b> | 0              | 178           | 58             | 146 493       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Ergotamine tartrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.7143 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 75.4237 % (> 74.1525 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22361     | 22361               | 0.00                         | 54.25                           |
| 22722     | 22361               | 13.12                        | 60.53                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe

von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Erythromycin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20011-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Erythromycin; Erythromycinum

### Special notes

When selecting the *Erythromycin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Erythromycin*:

| Supplier | Substance    | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------|------------------|-----------|---------|-------------|
| Fagron   | Erythromycin | 12E24-N04        | 21056     | 40      | 20120607    |
| Caelo    | Erythromycin | 13175601         | 21323     | 40      | 20130620    |
| Euro OTC | Erythromycin | 1308016-02       | 21651     | 40      | 1412542     |
| Fagron   | Erythromycin | 14B06-B35-290872 | 21669     | 40      | 20140225    |
| Euro OTC | Erythromycin | 1508034          | 21890     | 40      | 20150925*   |

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| Supplier | Substance    | Batch   | Sample ID | Spectra | Certificate |
|----------|--------------|---------|-----------|---------|-------------|
| Caelo    | Erythromycin | 160792  | 22438     | 40      | 20160408*   |
| Euro OTC | Erythromycin | 1607038 | 22832     | 40      | 20160831*   |
| Euro OTC | Erythromycin | 1705038 | 23438     | 40      | 20170705*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 320 spectra of 8 reference samples from the substance/substance group *Erythromycin*. These samples are listed above in the [calibration samples](#) section.
- 71066 spectra from a total of 1544 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 563 spectra of 12 reference samples from the substance/substance group *Erythromycin*.

| Supplier | Substance    | Batch            | Sample ID          | Spectra |
|----------|--------------|------------------|--------------------|---------|
| Caelo    | Erythromycin | 81907518         | 20011              | 80      |
| Caelo    | Erythromycin | 10006107         | 20107              | 40      |
| Fagron   | Erythromycin | pending          | 21011              | 90      |
| Fagron   | Erythromycin | pending          | 21012              | 50      |
| Euro OTC | Erythromycin | 1308016-02       | 21651 <sup>†</sup> | 20      |
| Fagron   | Erythromycin | 14B06-B35-290872 | 21669 <sup>†</sup> | 20      |
| Euro OTC | Erythromycin | 1508034          | 21890 <sup>†</sup> | 20      |
| Caelo    | Erythromycin | 160792           | 22438 <sup>†</sup> | 20      |
| Caelo    | Erythromycin | 160795           | 22439              | 60      |
| Caelo    | Erythromycin | 160797           | 22440              | 60      |
| Caelo    | Erythromycin | 160796           | 22442              | 60      |
| Fagron   | Erythromycin | 14B06-B35-290872 | 21669SI            | 43      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 166 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1424 spectra from 328 *Apo-Ident* customers from 364 batches from the substance/substance group *Erythromycin*.

| Supplier                | Substance    | Batch      | Spectra |
|-------------------------|--------------|------------|---------|
| Caelo                   | Erythromycin | 3092014B   | 1       |
| Caelo                   | Erythromycin | 3081601    | 1       |
| Caelo                   | Erythromycin | 5052015D   | 1       |
| Caelo                   | Erythromycin | 10079203   | 1       |
| Caelo                   | Erythromycin | 10091502   | 1       |
| Caelo                   | Erythromycin | 11195402   | 6       |
| Fagron                  | Erythromycin | 11D13-N09  | 3       |
| Caelo                   | Erythromycin | 120503601  | 1       |
| Caelo / Noweda          | Erythromycin | 1205036-02 | 1       |
| Caelo                   | Erythromycin | 12156206   | 2       |
| Caelo                   | Erythromycin | 12156208   | 7       |
| Euro OTC                | Erythromycin | 1308016-01 | 25      |
| Caelo                   | Erythromycin | 1308016-01 | 4       |
| Euro OTC                | Erythromycin | 130801601  | 6       |
| EuRho                   | Erythromycin | 1308016-01 | 4       |
| GEHE 21.05.2014         | Erythromycin | 1308016-01 | 1       |
| euroct/gehe             | Erythromycin | 1308016-01 | 1       |
| Euro OTC                | Erythromycin | 1308016-02 | 26      |
| euroct/gehe             | Erythromycin | 1308016-02 | 2       |
| EuRho                   | Erythromycin | 1308016-02 | 2       |
| Caelo                   | Erythromycin | 1308016-02 | 1       |
| EuRho/Phönix            | Erythromycin | 1308016-02 | 1       |
| Euro OTC                | Erythromycin | 130801602  | 2       |
| Gehe                    | Erythromycin | 1308016-02 | 1       |
| Noweda                  | Erythromycin | 130801602  | 2       |
|                         | Erythromycin | 1308016-02 | 1       |
| Euro OTC                | Erythromycin | 1308016-1  | 1       |
| Adler Anzag 26.05.14    | Erythromycin | 13081601   | 1       |
| Caelo                   | Erythromycin | 1315802    | 1       |
| Caelo                   | Erythromycin | 13175502   | 8       |
| Caelo                   | Erythromycin | 13175503   | 9       |
| Caelo                   | Erythromycin | 13175505   | 4       |
| Caelo                   | Erythromycin | 13175506   | 3       |
| Caelo                   | Erythromycin | 13175601   | 8       |
| Raben-Apotheke Mildenau | Erythromycin | 13175601   | 2       |
| Audor Pharma            | Erythromycin | 13175602   | 1       |
| Caelo                   | Erythromycin | 13175604   | 7       |
| PHOENIX 08.05.2014      | Erythromycin | 13175604   | 1       |
| Caelo                   | Erythromycin | 13175607   | 9       |
| Caelo                   | Erythromycin | 13175608   | 6       |
| gehe                    | Erythromycin | 13175607   | 1       |
| Noweda                  | Erythromycin | 13175608   | 1       |
| Fagron                  | Erythromycin | 13175608   | 1       |
| Gutenberg-Apotheke      | Erythromycin | 13175608   | 1       |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|----------------------------|------------------|-------------------|----------------|
| PHOENIX 08.05.2014         | Erythromycin     | 13175608          | 2              |
| Caelo                      | Erythromycin     | 13175611          | 3              |
| Caesar & Loretz            | Erythromycin     | 13175610          | 2              |
| Caelo                      | Erythromycin     | 13175801          | 12             |
| Caelo                      | Erythromycin     | 13175802          | 9              |
| Caelo                      | Erythromycin     | 13175803          | 7              |
| Caelo                      | Erythromycin     | 13175804          | 2              |
| Caelo                      | Erythromycin     | 13175808          | 3              |
| Caelo                      | Erythromycin     | 13175809          | 8              |
| Caelo                      | Erythromycin     | 13175810          | 4              |
| Caelo                      | Erythromycin     | 13175811          | 7              |
| Caelo                      | Erythromycin     | 13178756tzgklhj   | 1              |
| Caelo                      | Erythromycin     | 13D30-N01         | 6              |
| Fagron                     | Erythromycin     | 13D30-N01         | 25             |
| Fagron                     | Erythromycin     | 13F12-N21         | 32             |
| Alliance Health 28.01.2... | Erythromycin     | 13F12-N21         | 1              |
| Fagron                     | Erythromycin     | 13H22-N070228/246 | 1              |
| Caelo                      | Erythromycin     | 13H22-N07         | 1              |
| Fagron                     | Erythromycin     | 13H22-N07         | 8              |
| Caelo                      | Erythromycin     | 14/30-B01-300059  | 1              |
| Fagron                     | Erythromycin     | 14/30-B01         | 1              |
| Fagron                     | Erythromycin     | 13H22-N07         | 1              |
| Fagron                     | Erythromycin     | 14/30-B01-308789  | 3              |
| Fagron                     | Erythromycin     | 14/30-B01-300060  | 1              |
| Fagron                     | Erythromycin     | 14/30-B01-303884  | 1              |
| Fagron                     | Erythromycin     | 14/30B0130050     | 1              |
| Caelo                      | Erythromycin     | 14/30-B01-308189  | 2              |
| Fagron                     | Erythromycin     | 1430-B01-303884   | 1              |
| Fagron                     | Erythromycin     |                   | 2              |
| Caelo                      | Erythromycin     |                   | 2              |
| Caelo                      | Erythromycin     | 140044203         | 1              |
| Caelo                      | Erythromycin     | 140440006         | 1              |
| Caelo                      | Erythromycin     | 14044001          | 15             |
| Fagron                     | Erythromycin     | 14044001          | 1              |
| Caelo                      | Erythromycin     | 14044002          | 11             |
| AHD 02.02.15 EK 20,08      | Erythromycin     | 14044002          | 1              |
| Caelo                      | Erythromycin     | 14044004          | 6              |
| Caelo                      | Erythromycin     | 14044005          | 7              |
| Caelo                      | Erythromycin     | 140440044         | 1              |
| Caelo                      | Erythromycin     | 14044006          | 6              |
| Noweda                     | Erythromycin     | 14044006          | 1              |
| Eigenherstellung           | Erythromycin     | 14044006          | 1              |
| Caelo                      | Erythromycin     | 14044007          | 5              |
| Caelo                      | Erythromycin     | 14044008          | 6              |
| Caelo                      | Erythromycin     | 14044009          | 1              |
| Caelo                      | Erythromycin     | 14044010          | 6              |
| Caelo                      | Erythromycin     | 14044011          | 1              |
| Caelo                      | Erythromycin     | 14044014          | 2              |
| Caelo                      | Erythromycin     | 1404409           | 1              |
| Caelo                      | Erythromycin     | 14044101          | 6              |
| Caelo                      | Erythromycin     | 14044105          | 2              |
| Phoenix                    | Erythromycin     | 14044106          | 1              |
| Caelo                      | Erythromycin     | 14044107          | 1              |
| Caelo                      | Erythromycin     | 14044109          | 4              |
| Caelo                      | Erythromycin     | 14044108          | 1              |
| Caelo                      | Erythromycin     | 14044110          | 2              |
| Noweda21.04.2015           | Erythromycin     | 14044110          | 1              |
| Caelo                      | Erythromycin     | 14044114          | 5              |
| Caelo                      | Erythromycin     | 14044115          | 4              |
| Caelo                      | Erythromycin     | 14044118          | 3              |

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| <b>Supplier</b>  | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|------------------|------------------|-------------------|----------------|
| Caelo            | Erythromycin     | 14044201          | 5              |
| Phönix           | Erythromycin     | 14044201          | 1              |
| Caelo            | Erythromycin     | 14044202          | 2              |
| Caelo            | Erythromycin     | 14044205          | 5              |
| Euro OTC         | Erythromycin     | 14044205          | 1              |
| Caelo            | Erythromycin     | 14044206          | 3              |
| Caelo            | Erythromycin     | 14044207          | 5              |
| Euro OTC         | Erythromycin     | 140901901         | 5              |
| Euro OTC         | Erythromycin     | 1409019-01        | 20             |
| OTG/Gehe         | Erythromycin     | 1409019-01        | 1              |
| Phoenix goettin  | Erythromycin     | 1409019-01        | 1              |
| Caelo            | Erythromycin     | 1409019-01        | 2              |
| Euro OTC         | Erythromycin     | 1409019-02        | 30             |
| Euro OTC         | Erythromycin     | 1409019-01Mg100g  | 1              |
| Euro OTC         | Erythromycin     | 140901902         | 1              |
| Caelo            | Erythromycin     | 1409019-02        | 2              |
| EurPS            | Erythromycin     | 1409019-02        | 3              |
| Fagron           | Erythromycin     | 1409019-02        | 1              |
| EuroTOC / Noweda | Erythromycin     | 1409019-02        | 1              |
| Caelo            | Erythromycin     | 140901902         | 1              |
| Unisan           | Erythromycin     | 140901902         | 1              |
| Caelo            | Erythromycin     | 1414M-01362       | 1              |
| Euro OTC         | Erythromycin     | 140919-02         | 1              |
| Euro OTC         | Erythromycin     | 14090-9-01        | 1              |
| Caelo            | Erythromycin     | 1430b01300059     | 1              |
| Fagron           | Erythromycin     | 1430-b01-300060   | 1              |
| Fagron           | Erythromycin     | 1430B01303884     | 1              |
| Fagron           | Erythromycin     | 1430-B01-308789   | 1              |
| Fagron           | Erythromycin     | 14B06-B35         | 12             |
| Fagron           | Erythromycin     | 14B06-35-290873   | 1              |
| Phönix           | Erythromycin     | 14B06-B35         | 1              |
| Caelo            | Erythromycin     | 14B06-B35         | 2              |
| Fagron           | Erythromycin     | 14B06-B35-290866  | 4              |
| Fagron           | Erythromycin     | 14B06-B35-290872  | 8              |
| Caelo            | Erythromycin     | 14B06-B35-290872  | 2              |
| Fagron           | Erythromycin     | 14B06-B35-290873  | 4              |
| Fagron           | Erythromycin     | 14B06-B35290873   | 1              |
| Caelo            | Erythromycin     | 14B06-B35-290873  | 1              |
| Fagron           | Erythromycin     | 14B06-B35-290874  | 3              |
| Fagron           | Erythromycin     | 14B06-B35-290875  | 8              |
| Fagron           | Erythromycin     | 14B06-B35-293508  | 2              |
| Caelo            | Erythromycin     | 14b06-b35-293508  | 1              |
| Noweda/Gehe      | Erythromycin     | 14B06-B35-293508  | 1              |
| Fagron           | Erythromycin     | 14B06-B35-293509  | 7              |
| Fagron           | Erythromycin     | 14b06-b35-293509  | 1              |
| Fagron           | Erythromycin     | 14Bo6-B35         | 1              |
| Fagron           | Erythromycin     | 14F13-B02         | 2              |
| Bombastus        | Erythromycin     | 14F13-B02         | 1              |
| Fagron           | Erythromycin     | 14F13-B02-293488  | 1              |
| Fagron           | Erythromycin     | 14F13-B02-293487  | 1              |
| Fagron           | Erythromycin     | 14F13-B02-293490  | 2              |
| Fagron           | Erythromycin     | 14F13-B02-293511  | 3              |
| Caelo            | Erythromycin     | 14F13-B02-296464  | 2              |
| Fagron           | Erythromycin     | 14F13-B02-300061  | 3              |
| Fagron           | Erythromycin     | 14F13-B02-296464  | 2              |
| Fagron           | Erythromycin     | 14F13-B12-300061  | 1              |
| Fagron           | Erythromycin     | 14I30-B01         | 9              |
| Caelo            | Erythromycin     | 14I30-B01         | 1              |
| Fagron           | Erythromycin     | 14I30B01          | 1              |
| Fagron           | Erythromycin     | 14I30-B01-3000060 | 1              |

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| Supplier                  | Substance    | Batch            | Spectra |
|---------------------------|--------------|------------------|---------|
| Fagron                    | Erythromycin | 14I30-B01-300050 | 2       |
| Fagron                    | Erythromycin | 14I30-B01-300060 | 1       |
| Fagron                    | Erythromycin | 14i30b01-300059  | 1       |
| Fagron                    | Erythromycin | 14I30-B01-300062 | 2       |
| Fagron                    | Erythromycin | 14I30-B01-303884 | 6       |
| Fagron                    | Erythromycin | 14i30-b01-303884 | 1       |
| Fagron                    | Erythromycin | 14I30-B01-306927 | 2       |
| Fagron                    | Erythromycin | 14I30-B01-308188 | 3       |
| Fagron                    | Erythromycin | 14I30-B01-308189 | 1       |
| Fagron                    | Erythromycin | 14I30B01308189   | 1       |
| Fagron                    | Erythromycin | 14I30-B01-308789 | 1       |
| AHD 26.02.16 13,15EUR     | Erythromycin | 14I30-B01-308789 | 1       |
| Fagron                    | Erythromycin | 14I30-B01-311166 | 2       |
| Fagron                    | Erythromycin | 14i30-b01-311166 | 1       |
| Caelo                     | Erythromycin | 15042601         | 4       |
| Caelo                     | Erythromycin | 15042602         | 3       |
| caesar&lorenz,phönix      | Erythromycin | 15042603         | 1       |
| Caelo                     | Erythromycin | 15042603         | 5       |
| Bombastus                 | Erythromycin | 15042603         | 1       |
| Caelo                     | Erythromycin | 15042604         | 3       |
| Calo/AHD                  | Erythromycin | 15042605         | 1       |
| Caelo                     | Erythromycin | 15042605         | 3       |
| Caelo                     | Erythromycin | 15042608         | 2       |
| Caelo                     | Erythromycin | 15042609         | 5       |
| Phoenix                   | Erythromycin | 15042609         | 1       |
| Caelo                     | Erythromycin | 15042610         | 4       |
| Caesar&Loretz GmbH /Anzag | Erythromycin | 15042610         | 1       |
| Caelo                     | Erythromycin | 15042611         | 2       |
| Caelo                     | Erythromycin | 15042612         | 5       |
| Caelo                     | Erythromycin | 15042613         | 2       |
| Caelo                     | Erythromycin | 15042701         | 6       |
| Caelo                     | Erythromycin | 15042702         | 5       |
| Caelo                     | Erythromycin | 15042703         | 7       |
| Caelo                     | Erythromycin | 15042704         | 8       |
| Caelo                     | Erythromycin | 15042705         | 6       |
| Caelo                     | Erythromycin | 15042706         | 4       |
| Caelo                     | Erythromycin | 15042707         | 1       |
| Caelo                     | Erythromycin | 15042708         | 1       |
| Caelo                     | Erythromycin | 15042711         | 6       |
| Caelo                     | Erythromycin | 15042802         | 1       |
| Caelo                     | Erythromycin | 15042803         | 10      |
| Rondell Apotheke          | Erythromycin | 15042803         | 1       |
| Caelo                     | Erythromycin | 15042804         | 1       |
| Caelo                     | Erythromycin | 15042806         | 5       |
| Caesar&Loretz GmbH        | Erythromycin | 15042807         | 1       |
| Caelo                     | Erythromycin | 15042809         | 1       |
| Euro OTC                  | Erythromycin | 15042810         | 1       |
| Caelo                     | Erythromycin | 15042810         | 1       |
| Phoenix                   | Erythromycin | 15042811         | 1       |
| Caelo                     | Erythromycin | 15042811         | 1       |
| Caelo                     | Erythromycin | 15042813         | 7       |
| Caesar & Loretz/AHC       | Erythromycin | 15042813         | 1       |
| Caelo                     | Erythromycin | 15042815         | 2       |
| Caelo                     | Erythromycin | 15042814         | 3       |
| Caelo                     | Erythromycin | 15042901         | 5       |
| Euro OTC                  | Erythromycin | 15080-01         | 1       |
| Euro OTC                  | Erythromycin | 1508034-01       | 25      |
| Euro/Gehe                 | Erythromycin | 1508034-01       | 1       |
| Caelo                     | Erythromycin | 1508034-01       | 2       |
| Fagron                    | Erythromycin | 1508034-01       | 1       |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------|------------------|----------------|
| Caelo                      | Erythromycin     | 150803401        | 1              |
| Noweda                     | Erythromycin     | 150803401        | 1              |
| Euro OTC                   | Erythromycin     | 1508034-02       | 9              |
| Caelo                      | Erythromycin     | 1508034-02       | 1              |
| Euro OTC                   | Erythromycin     | 1508034-02Mg100g | 1              |
| Caelo                      | Erythromycin     | 1524004          | 1              |
| Caelo                      | Erythromycin     | 15245002         | 10             |
| Caelo                      | Erythromycin     | 15245003         | 6              |
| EuRho/Sanacorp             | Erythromycin     | 15245004         | 1              |
| Caelo                      | Erythromycin     | 15245004         | 6              |
| Wolff/AHD                  | Erythromycin     | 15245004         | 1              |
| Gehe                       | Erythromycin     | 15245004         | 1              |
| Caelo                      | Erythromycin     | 15245005         | 1              |
| Caelo                      | Erythromycin     | 15245007         | 1              |
| Caelo                      | Erythromycin     | 15245008         | 1              |
| Caelo                      | Erythromycin     | 15245101         | 8              |
| Noweda                     | Erythromycin     | 15245101         | 1              |
| Caelo                      | Erythromycin     | 154042602        | 1              |
| Fagron                     | Erythromycin     | 15G07-B05-312356 | 2              |
| Fagron                     | Erythromycin     | 16/24-B10-329158 | 1              |
| Jenapharm/Phönix           | Erythromycin     | 1607036-01       | 1              |
| Euro OTC                   | Erythromycin     | 1607038-01       | 25             |
| Caelo                      | Erythromycin     | 160703801        | 1              |
| Euro OTC                   | Erythromycin     | 160703801        | 2              |
| VDL                        | Erythromycin     | 160703801        | 1              |
| Biomed/Phönix              | Erythromycin     | 1607038-01       | 1              |
| Caelo                      | Erythromycin     | 1607038-02       | 3              |
| Euro OTC                   | Erythromycin     | 1607038-02       | 4              |
| Gehe                       | Erythromycin     | 1607038-02       | 1              |
| Euro OTC                   | Erythromycin     | 160703802        | 2              |
| Caelo                      | Erythromycin     | 16079201         | 3              |
| Caelo                      | Erythromycin     | 16079202         | 4              |
| Caelo                      | Erythromycin     | 16079203         | 8              |
| Caelo                      | Erythromycin     | 16079204         | 4              |
| Gehe                       | Erythromycin     | 16079204         | 1              |
| Phönix                     | Erythromycin     | 16079205         | 1              |
| Caelo                      | Erythromycin     | 16079205         | 4              |
| Alte Apotheke              | Erythromycin     | 16079206         | 1              |
| Caesar & Loretz GmbH, P... | Erythromycin     | 16079207         | 1              |
| Caelo                      | Erythromycin     | 16079207         | 1              |
| Caelo                      | Erythromycin     | 16079206         | 1              |
| Caelo                      | Erythromycin     | 16079208         | 2              |
| Fagron                     | Erythromycin     | 16079208         | 1              |
| Caelo                      | Erythromycin     | 16079210         | 1              |
| Caelo                      | Erythromycin     | 16079213         | 6              |
| Gehe                       | Erythromycin     | 16079209         | 1              |
| Caelo                      | Erythromycin     | 16079214         | 2              |
| Caelo                      | Erythromycin     | 16079216         | 2              |
| Caelo                      | Erythromycin     | 16079501         | 2              |
| Caelo                      | Erythromycin     | 16079502         | 2              |
| Phoenix                    | Erythromycin     | 16079501         | 1              |
| Caelo                      | Erythromycin     | 16079510         | 2              |
| Caelo                      | Erythromycin     | 16079503         | 1              |
| Caelo                      | Erythromycin     | 16079511         | 1              |
| Caelo                      | Erythromycin     | 16079513         | 3              |
| Caelo                      | Erythromycin     | 16079608         | 1              |
| Fagron                     | Erythromycin     | 16G06-B03        | 3              |
| Fagron                     | Erythromycin     | 16G06-B030003    | 1              |
| Fagron                     | Erythromycin     | 16G06-B03-324463 | 5              |
| Fagron                     | Erythromycin     | 16g06-b03-324463 | 1              |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------|------------------|----------------|
| Fagron                     | Erythromycin     | 16G06-B03-324464 | 6              |
| Fagron                     | Erythromycin     | 16G06-B03-329150 | 1              |
| Fagron                     | Erythromycin     | 16G06-B03-324465 | 1              |
| Fagron                     | Erythromycin     | 16G06-B03-324466 | 2              |
| Fagron                     | Erythromycin     | 16G06B03-329149  | 1              |
| Fagron                     | Erythromycin     | 16J24-B10-329154 | 1              |
| Caelo                      | Erythromycin     | 24071402         | 1              |
| Caelo                      | Erythromycin     | 28041505         | 1              |
| Caelo                      | Erythromycin     | 28101405         | 1              |
| Caelo                      | Erythromycin     | 30011505         | 1              |
| Fagron                     | Erythromycin     | 3000-50          | 1              |
| Caelo                      | Erythromycin     | 5042604          | 1              |
| Sanacorp                   | Erythromycin     | 59/AKD51         | 1              |
| Caelo                      | Erythromycin     | 60/AKD4          | 1              |
| Sanacorp                   | Erythromycin     | 60/AKD52         | 1              |
| Sanacorp                   | Erythromycin     |                  | 1              |
| Fagron                     | Erythromycin     | EB022E14         | 3              |
| Caelo                      | Erythromycin     | EB06/14          | 1              |
| Fagron                     | Erythromycin     | EB032J13         | 4              |
| Fagron                     | Erythromycin     | EB068/14         | 1              |
| Klenk                      | Erythromycin     | EB068I14         | 1              |
| Fagron                     | Erythromycin     | EB06814          | 1              |
| Caelo                      | Erythromycin     | eb078b13         | 1              |
| Euro OTC                   | Erythromycin     | EBS/1307-BM-001  | 1              |
| Euro OTC                   | Erythromycin     | EBS/1408-BM-001  | 1              |
| Fagron                     | Erythromycin     | OEBA/0010516     | 2              |
| Caelo                      | Erythromycin     | 511111           | 1              |
| Fagron                     | Erythromycin     | 510211362        | 1              |
| Euro OTC                   | Erythromycin     | 80616-4          | 1              |
| Caelo                      | Erythromycin     | 10006206         | 1              |
| Caelo                      | Erythromycin     | 1021703          | 1              |
| Euro OTC                   | Erythromycin     | 1013u-01362      | 1              |
| Caelo                      | Erythromycin     | 10217101         | 1              |
| Caelo                      | Erythromycin     | 10217102         | 1              |
| Caelo                      | Erythromycin     | 10217103         | 1              |
| Caelo                      | Erythromycin     | 10217105         | 1              |
| Caelo                      | Erythromycin     | 10217106         | 1              |
| Caelo                      | Erythromycin     | 10217204         | 1              |
| Caelo                      | Erythromycin     | 10217107         | 1              |
| Caesar & Loretz GmbH, 4... | Erythromycin     | 10217208         | 1              |
| Caelo                      | Erythromycin     | 10217501         | 1              |
| Caelo                      | Erythromycin     | 10217412         | 1              |
| Fagron                     | Erythromycin     | 11/06-N05        | 1              |
| Erika apotheke             | Erythromycin     | 11/06-N05        | 1              |
| Sanacorp                   | Erythromycin     | 1106036-04       | 1              |
| Euro OTC                   | Erythromycin     | 1106036-04       | 2              |
| Phönix Gotha               | Erythromycin     | 1106036-04       | 1              |
| Euro OTC                   | Erythromycin     | 1106036-05       | 6              |
| Phönix Gotha               | Erythromycin     | 1106036-05       | 1              |
| Fagron                     | Erythromycin     | 1106036-05       | 3              |
| Europharm/Otto             | Erythromycin     | 1106036-05       | 2              |
| Gehe                       | Erythromycin     | 1106036-05       | 1              |
| EuRho/Phönix               | Erythromycin     | 1106036-05       | 1              |
| Caelo                      | Erythromycin     | 11195302         | 2              |
| Caelo                      | Erythromycin     | 1114Q-01362      | 1              |
| Phönix 30.08.2012          | Erythromycin     | 11195305         | 1              |
| Caelo                      | Erythromycin     | 11195306         | 1              |
| Caelo                      | Erythromycin     | 11195404         | 2              |
| Caelo                      | Erythromycin     | 11195405         | 3              |
| Caelo                      | Erythromycin     | 11195406         | 1              |

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| <b>Supplier</b>         | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|-------------------------|------------------|--------------|----------------|
| Caelo                   | Erythromycin     | 11195407     | 4              |
| VDL                     | Erythromycin     | 11195407     | 1              |
| Noweda                  | Erythromycin     | 11195411     | 2              |
| Gehe                    | Erythromycin     | 11195412     | 1              |
| Caelo                   | Erythromycin     | 11195408     | 1              |
| Caelo                   | Erythromycin     | 11195412     | 1              |
| Noweda                  | Erythromycin     | 11195413     | 1              |
| Phoenix, 13.09.2012     | Erythromycin     | 1195305      | 1              |
| Caelo                   | Erythromycin     | 1195306      | 1              |
| Fagron                  | Erythromycin     | 11J06-N05    | 3              |
| Fagron                  | Erythromycin     | 11j06-n05    | 1              |
| Caelo                   | Erythromycin     | 1195407      | 1              |
| Caelo                   | Erythromycin     | 11j06-n05    | 1              |
| Gehe                    | Erythromycin     | 11D13-N09    | 1              |
| Post-Apotheke           | Erythromycin     | 11J06-N05    | 3              |
| Phönix Gotha            | Erythromycin     | 11J06-N05    | 1              |
| ANZAG am 16.05.2012     | Erythromycin     | 11J06-N05    | 1              |
| Fagron                  | Erythromycin     | 11J06-No5    | 1              |
| Phytocomm               | Erythromycin     | 1203ery      | 1              |
| EuRho/Phönix            | Erythromycin     | 1205035      | 1              |
| Anzag 23.11.12 ek:26,49 | Erythromycin     | 1205035-01   | 1              |
| Euro OTC                | Erythromycin     | 1205035-01   | 15             |
| EuRho                   | Erythromycin     | 1205035-01   | 1              |
| Phönix                  | Erythromycin     | 120503501    | 1              |
| Fagron                  | Erythromycin     | 1205035-01   | 1              |
| Euro OTC                | Erythromycin     | 1205035-02   | 19             |
| Caelo                   | Erythromycin     | 120503502    | 1              |
| Sanacorp                | Erythromycin     | 1205035-02   | 1              |
| Alliance Health         | Erythromycin     | 120503502    | 1              |
| EuRho                   | Erythromycin     | 1205035-02   | 1              |
| Euro OTC                | Erythromycin     | 120503502    | 1              |
| Euro OTC                | Erythromycin     | 1205036-01   | 7              |
| Euro OTC                | Erythromycin     | 120503601    | 1              |
| EuRho                   | Erythromycin     | 1205036-01   | 1              |
| Euro OTC                | Erythromycin     | 1205036-02   | 9              |
| Euro OTC                | Erythromycin     | 120503602    | 2              |
| Phönix 11.11.2013       | Erythromycin     | 1205036-02   | 1              |
| phönix                  | Erythromycin     | 1205036-02   | 1              |
| Phönix                  | Erythromycin     | 1205036-02   | 1              |
| Caelo                   | Erythromycin     | 12152101     | 3              |
| Caelo                   | Erythromycin     | 12152102     | 3              |
| Caelo                   | Erythromycin     | 12152103     | 3              |
| Caelo                   | Erythromycin     | 12152104     | 4              |
| Gehe                    | Erythromycin     | 12152103     | 1              |
| Gehe                    | Erythromycin     | 12152104     | 1              |
| Gehe                    | Erythromycin     | 12152105     | 1              |
| Caelo                   | Erythromycin     | 12152105     | 6              |
| Caelo                   | Erythromycin     | 12152107     | 1              |
| Noweda                  | Erythromycin     | 12152108     | 2              |
| Caelo                   | Erythromycin     | 12152108     | 5              |
| Caelo                   | Erythromycin     | 12152109     | 11             |
| Caelo                   | Erythromycin     | 1215219      | 1              |
| Noweda                  | Erythromycin     | 12152201     | 1              |
| Caelo                   | Erythromycin     | 12152201     | 8              |
| Phoenix                 | Erythromycin     | 12152201     | 2              |
| Caelo                   | Erythromycin     | 12152202     | 4              |
| Sanacorp                | Erythromycin     | 12152202     | 1              |
| Caelo                   | Erythromycin     | 12152203     | 1              |
| Caelo                   | Erythromycin     | 12152205     | 11             |
| Gehe 20.03.2013         | Erythromycin     | 12152205     | 1              |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|----------------------------|------------------|-------------------|----------------|
| Caelo                      | Erythromycin     | 12152206          | 11             |
| Caelo                      | Erythromycin     | 12152208          | 4              |
| Fagron                     | Erythromycin     | 12152209          | 1              |
| Caelo                      | Erythromycin     | 12156201          | 3              |
| AHD, 11.09.2013            | Erythromycin     | 12152210          | 1              |
| Caelo                      | Erythromycin     | 12156202          | 8              |
| Caelo                      | Erythromycin     | 12156203          | 2              |
| Caelo                      | Erythromycin     | 12156204          | 4              |
| Caelo                      | Erythromycin     | 12156207          | 4              |
| AHC 04.07.13 EK38,50       | Erythromycin     | 12156207          | 1              |
| Sanacorp                   | Erythromycin     | 12156208          | 1              |
| Fagron                     | Erythromycin     | 12e24-n04         | 1              |
| Fagron                     | Erythromycin     | 12E24-N04         | 19             |
| Noweda                     | Erythromycin     | 12E24-N04         | 2              |
| Anzag                      | Erythromycin     | 12e24-n04         | 1              |
| Gehe                       | Erythromycin     | 12E24-N04         | 1              |
| Großhandel                 | Erythromycin     | 12E24-N04         | 1              |
| Caelo                      | Erythromycin     | 12E24-N04         | 2              |
| Alliance Healthcare        | Erythromycin     | 12E24-N04         | 1              |
| Fagron                     | Erythromycin     | 12E24-No4         | 1              |
| Fagron                     | Erythromycin     | 12J30-N01         | 13             |
| Fagron                     | Erythromycin     | 12J30N01          | 1              |
| Phönix 27.04.2013          | Erythromycin     | 12J30-N01         | 1              |
| Fagron                     | Erythromycin     | 12J30-N01         | 1              |
| Euro                       | Erythromycin     | 1308016-02        | 1              |
| Caelo                      | Erythromycin     | 1315501           | 1              |
| Caelo                      | Erythromycin     | 13145504          | 1              |
| Caelo                      | Erythromycin     | 13175501          | 6              |
| gepepharm GmbH             | Erythromycin     | 13175502          | 1              |
| Fagron                     | Erythromycin     | 13175503          | 1              |
| Caelo                      | Erythromycin     | 13175504          | 6              |
| Anzag                      | Erythromycin     | 13175506          | 1              |
| Caelo                      | Erythromycin     | 131756017         | 1              |
| Caesar&loretz,Phoenix      | Erythromycin     | 13175602          | 1              |
| Caelo                      | Erythromycin     | 13175603          | 9              |
| Noweda                     | Erythromycin     | 13175603          | 2              |
| Euro CT Phönix             | Erythromycin     | 13175604          | 1              |
| Phoenix                    | Erythromycin     | 13175608          | 1              |
| Caelo                      | Erythromycin     | 13175612          | 1              |
| Fagron                     | Erythromycin     | 13175803          | 1              |
| Caelo                      | Erythromycin     | 13189001          | 6              |
| Gehe                       | Erythromycin     | 13189001          | 2              |
| Caesar & Loretz GmbH, 4... | Erythromycin     | 13189002          | 1              |
| Caelo                      | Erythromycin     | 13189002          | 7              |
| gehe 24.8.13               | Erythromycin     | 13189002          | 1              |
| Caelo                      | Erythromycin     | 13189004          | 5              |
| Caelo                      | Erythromycin     | 13189006          | 1              |
| Gehe                       | Erythromycin     | 13189004          | 1              |
| Caelo                      | Erythromycin     | 13189007          | 1              |
| Caeolo/Noweda              | Erythromycin     | 13189007          | 1              |
| Caelo                      | Erythromycin     | 132152108         | 1              |
| Fagron                     | Erythromycin     | 13A02-N06         | 9              |
| Caelo                      | Erythromycin     | 13A02-N06         | 1              |
| Fagron                     | Erythromycin     | 13A02N06          | 1              |
| post apotheke              | Erythromycin     | 13A02-N06         | 1              |
| Phönix, 28.10.2013         | Erythromycin     | 13A02-N06         | 1              |
| Fagron                     | Erythromycin     | 13A02-N-06        | 1              |
| fagr                       | Erythromycin     | 13A02-N06         | 1              |
| Fagron                     | Erythromycin     | 13A02-N060571/680 | 1              |
| Fagron                     | Erythromycin     | 13A02-No6         | 1              |

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| Supplier              | Substance    | Batch               | Spectra |
|-----------------------|--------------|---------------------|---------|
| Fagron                | Erythromycin | 13D30-N01003/456    | 1       |
| Fagron                | Erythromycin | 13D30-N010336/730   | 1       |
| GEHE                  | Erythromycin | 13D30-N01           | 1       |
| Fagron                | Erythromycin | 13d30-n01           | 1       |
| Fagron                | Erythromycin | 13d30-N01           | 1       |
| Fagron                | Erythromycin | 13D30N01            | 1       |
| AHD, 25.07.2013       | Erythromycin | 13D30-N01           | 1       |
| Fagron                | Erythromycin | 13D30-N010278/730   | 1       |
| AHD, 25.11.13         | Erythromycin | 13F12-N21           | 1       |
| Alliance Healthcare   | Erythromycin | 13F12-N21           | 1       |
| Gehe                  | Erythromycin | 13F12-N21           | 1       |
| Fagron                | Erythromycin | 13H22-N070126/246   | 1       |
| Sanacorp              | Erythromycin | 13H22-N07           | 1       |
| Caesar&lorenz,Phoenix | Erythromycin | 14044004            | 1       |
| Caelo                 | Erythromycin | 1404414             | 1       |
| Euro OT               | Erythromycin | 1409019-02          | 1       |
| Caelo                 | Erythromycin | 16071302            | 1       |
| Caelo                 | Erythromycin | 19071306            | 1       |
| EuRho/Noweda          | Erythromycin | 1508034-02          | 1       |
| Caelo                 | Erythromycin | 20122013D           | 1       |
| Caelo                 | Erythromycin | 22041302            | 1       |
| Caelo                 | Erythromycin | 20270912-3          | 1       |
| Caelo                 | Erythromycin | 25011304            | 1       |
| Caelo                 | Erythromycin | 24101312            | 1       |
| Caelo                 | Erythromycin | 26011402            | 1       |
| Caelo                 | Erythromycin | 26101204            | 1       |
| Caelo                 | Erythromycin | 27131-01362         | 1       |
| Caelo                 | Erythromycin | 27071202            | 1       |
| Caelo                 | Erythromycin | 3110195             | 1       |
| Euro OTC              | Erythromycin | 3613A1362           | 1       |
| Euro OTC              | Erythromycin | 4112Q-01362         | 1       |
| Fagron                | Erythromycin | 4212E-01362         | 1       |
| Caelo                 | Erythromycin | 59/AKD59            | 1       |
| Euro OTC              | Erythromycin | 700770              | 1       |
| Fagron                | Erythromycin | E-030613-1          | 1       |
| Fagron                | Erythromycin | E-250213-2          | 1       |
| Fagron                | Erythromycin | EB048G12            | 1       |
| Fagron                | Erythromycin | EB078B13            | 1       |
| Fagron                | Erythromycin | EBS/1201-008        | 2       |
| Euro OTC              | Erythromycin | EBS/1205-M-040      | 1       |
| Euro OTC              | Erythromycin | EBS/1205-M-041      | 1       |
| Phagron               | Erythromycin |                     | 1       |
| Fagron                | Erythromycin | 11195302            | 1       |
| Caelo                 | Erythromycin | 11195411            | 1       |
| Anzag                 | Erythromycin | 12152206            | 1       |
| Symbiotica            | Erythromycin | 12152201            | 1       |
| Euro OTC              | Erythromycin | 12A02-N06           | 1       |
| Caelo                 | Erythromycin | 13175504-3413310132 | 1       |
| Caelo                 | Erythromycin | 13175506-3559412014 | 1       |
| AHD                   | Erythromycin | 13189002            | 1       |

- 68 209 spectra from 414 *Apo-Ident* customers from a total of 23 440 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Erythromycin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Erythromycin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 320           | 0              | 71 066        |
| Type B | 0              | 561           | 2              | 146 166       |
| Type C | 0              | 1382          | 42             | 68 209        |

The substance/substance group *Erythromycin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.1250 %) |
| Type B | 100.0000 % (> 99.9923 %) | 99.6448 % (> 99.1119 %)  |
| Type C | 100.0000 % (> 99.8812 %) | 97.0506 % (> 96.8399 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21056     | 21890               | 6.75                         | 41.88                           |
| 21323     | 21890               | 4.79                         | 42.09                           |
| 21651     | 21651               | 0.00                         | 36.93                           |
| 21669     | 21651               | 10.58                        | 37.21                           |
| 21890     | 21890               | 0.00                         | 41.71                           |
| 22438     | 22438               | 0.00                         | 43.93                           |
| 22832     | 22832               | 0.00                         | 38.83                           |
| 23438     | 23438               | 0.00                         | 36.98                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können

aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Estradiol benzoate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20098-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Estradiol benzoate; Estradioli benzoas; Oestradiolum benzoicum

### Special notes

When selecting the *Estradiol benzoate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Estradiol benzoate*:

| Supplier | Substance          | Batch      | Sample ID | Spectra | Certificate |
|----------|--------------------|------------|-----------|---------|-------------|
| Fagron   | Estradiol benzoate | 12H02-N02  | 20889     | 40      | 20120817    |
| Fagron   | Estradiol benzoate | 14B20-B02  | 21257     | 40      | 20140327    |
| Euro OTC | Estradiol benzoate | 1301006-02 | 21290     | 40      | 1507405     |
| Euro OTC | Estradiol benzoate | 1507009    | 21869     | 40      | 0000010566  |
| Caello   | Estradiol benzoate | 15078608   | 23218     | 40      | 20150415    |

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| Supplier | Substance          | Batch     | Sample ID | Spectra | Certificate |
|----------|--------------------|-----------|-----------|---------|-------------|
| Fagron   | Estradiol benzoate | 12H02-N02 | 20889SI   | 40      | 20120817    |
| Fagron   | Estradiol benzoate | 14B20-B02 | 21257SI   | 40      | 20140327    |
| Euro OTC | Estradiol benzoate | 1507009   | 21869SI   | 40      | 0000010566  |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 320 spectra of 8 reference samples from the substance/substance group *Estradiol benzoate*. These samples are listed above in the [calibration samples](#) section.
- 71 066 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 8 reference samples from the substance/substance group *Estradiol benzoate*.

| Supplier | Substance          | Batch     | Sample ID            | Spectra |
|----------|--------------------|-----------|----------------------|---------|
| Caelo    | Estradiol benzoate | 13277607  | 21324                | 40      |
| Euro OTC | Estradiol benzoate | 1507009   | 21869 <sup>†</sup>   | 20      |
| Euro OTC | Estradiol benzoate | 1611004   | 22873                | 40      |
| Fagron   | Estradiol benzoate | 12H02-N02 | 20889SI <sup>†</sup> | 20      |
| Fagron   | Estradiol benzoate | 14B20-B02 | 21257SI <sup>†</sup> | 20      |
| Euro OTC | Estradiol benzoate | 1507009   | 21869SI <sup>†</sup> | 20      |
| Euro OTC | Estradiol benzoate | 1611004   | 22873SI              | 40      |
| Caelo    | Estradiol benzoate | 15078608  | 23218SI              | 40      |

- 146 489 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 261 spectra from 149 *Apo-Ident* customers from 74 batches from the substance/substance group *Estradiol benzoate*.

| Supplier                   | Substance          | Batch             | Spectra |
|----------------------------|--------------------|-------------------|---------|
| Caelo                      | Estradiol benzoate | 1149              | 1       |
| Caelo                      | Estradiol benzoate | 1201019-02        | 1       |
| Euro OTC                   | Estradiol benzoate | 1201019-01        | 7       |
| Fagron                     | Estradiol benzoate | 12D20N06          | 1       |
| Euro OTC                   | Estradiol benzoate | 1301006-02        | 8       |
| Caelo                      | Estradiol benzoate | 13276401          | 6       |
| Caelo                      | Estradiol benzoate | 13277605          | 5       |
| Caelo                      | Estradiol benzoate | 13277607          | 3       |
| Fagron                     | Estradiol benzoate | 13C15-B07-288645  | 1       |
| Euro OTC                   | Estradiol benzoate | 14010001-01       | 1       |
| Euro OTC                   | Estradiol benzoate | 1401001-01        | 10      |
| Caelo                      | Estradiol benzoate | 1401001-01        | 1       |
| Euro OTC                   | Estradiol benzoate | 140101-01         | 1       |
| Euro OTC                   | Estradiol benzoate | 1412033-01        | 7       |
| Fagron                     | Estradiol benzoate | 1412033-01        | 1       |
| Fagron                     | Estradiol benzoate | 14B20-B02         | 3       |
| Fagron                     | Estradiol benzoate | 14B20-B02-292001  | 3       |
| AHD                        | Estradiol benzoate | 14B20-B02-292001  | 1       |
| Fagron                     | Estradiol benzoate | 14B20-B02-2920001 | 1       |
| Fagron                     | Estradiol benzoate | 14B20-B02-294949  | 5       |
| Caelo                      | Estradiol benzoate | 14B20-B02-294949  | 1       |
| phönix                     | Estradiol benzoate | 14B20-B02-294949  | 1       |
| Fagron                     | Estradiol benzoate | 14b20-b02-294949  | 1       |
| Euro OTC                   | Estradiol benzoate | 1507009-01        | 5       |
| Euro OTC                   | Estradiol benzoate | 150700901         | 2       |
| Caelo                      | Estradiol benzoate | 15078602          | 6       |
| Caelo                      | Estradiol benzoate | 15078603          | 11      |
| Caelo                      | Estradiol benzoate | 15078604          | 9       |
| Caelo                      | Estradiol benzoate | 15078606          | 3       |
| Gehe                       | Estradiol benzoate | 15078606          | 1       |
| Caelo                      | Estradiol benzoate | 15078608          | 2       |
| Fagron                     | Estradiol benzoate | 15C10-B04-305523  | 7       |
| Caelo                      | Estradiol benzoate | 15c10-b04-305523  | 1       |
| Caelo                      | Estradiol benzoate | 15C10B04305523    | 1       |
| Fagron                     | Estradiol benzoate | 15c10-b04-305523  | 1       |
| Caelo                      | Estradiol benzoate | 15C10-B04-305523  | 2       |
| Fagron                     | Estradiol benzoate | 15E08-B08-311705  | 7       |
| Fagron                     | Estradiol benzoate | 83101340          | 5       |
| Euro OTC                   | Estradiol benzoate | 83101340          | 1       |
| Euro OTC                   | Estradiol benzoate | 84303830          | 1       |
| Fagron                     | Estradiol benzoate | 84303830          | 2       |
| Caelo                      | Estradiol benzoate | 84303830          | 1       |
| Caelo                      | Estradiol benzoate |                   | 4       |
| Caelo                      | Estradiol benzoate | 6091305           | 1       |
| Sanacorp                   | Estradiol benzoate | 10/AKD24          | 1       |
| Euro OTC                   | Estradiol benzoate | 8011422           | 1       |
| Finze                      | Estradiol benzoate | 1003040-01        | 2       |
| Euro OTC                   | Estradiol benzoate | 1007037-02        | 1       |
| aliance healthcare 5.12... | Estradiol benzoate | 10118576          | 1       |
| Bayer-Schering             | Estradiol benzoate | 1007037-03        | 1       |
| euroho/gehe                | Estradiol benzoate | 1007037-02        | 1       |
| Caelo                      | Estradiol benzoate | 10124909          | 3       |

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| Supplier                   | Substance          | Batch            | Spectra |
|----------------------------|--------------------|------------------|---------|
| v.d.l                      | Estradiol benzoate | 10124913         | 1       |
| Caelo                      | Estradiol benzoate | 10124913         | 1       |
| Caelo                      | Estradiol benzoate | 10124912         | 1       |
| Caesar                     | Estradiol benzoate | 10124912         | 1       |
| Caelo                      | Estradiol benzoate | 10124915         | 2       |
| Caelo                      | Estradiol benzoate | 10124918         | 2       |
| Caelo                      | Estradiol benzoate | 10124919         | 1       |
| Caelo                      | Estradiol benzoate | 10124921         | 3       |
| Caelo                      | Estradiol benzoate | 11L23-N01        | 1       |
| Gehe                       | Estradiol benzoate | 11L23-N01        | 1       |
| Fagron                     | Estradiol benzoate | 11L23-N01        | 1       |
| Euro OTC                   | Estradiol benzoate | 1201019-02       | 12      |
| A.H. 07.06.13 ek: 24,14EUR | Estradiol benzoate | 1201019-02       | 1       |
| Phönix                     | Estradiol benzoate | 1201019-02       | 1       |
| EuRho/Sanacorp             | Estradiol benzoate | 1201019-02       | 1       |
| Euro OTC                   | Estradiol benzoate | 121019-01        | 1       |
| Caelo                      | Estradiol benzoate | 12255903         | 2       |
| Fagron                     | Estradiol benzoate | 12255903         | 1       |
| Caelo                      | Estradiol benzoate | 12255904         | 15      |
| Caelo                      | Estradiol benzoate | 12255905         | 15      |
| GEHE                       | Estradiol benzoate | 12H02-N02        | 1       |
| Fagron                     | Estradiol benzoate | 12h02-n02        | 2       |
| Fagron                     | Estradiol benzoate | 12H02-N02        | 4       |
| Fagron                     | Estradiol benzoate | 12H02-N052       | 1       |
| Fagron                     | Estradiol benzoate | 13/11-N01        | 2       |
| Fagron                     | Estradiol benzoate | 12L14-N02        | 1       |
| Euro OTC                   | Estradiol benzoate | 1301006-01       | 2       |
| Euro OTC                   | Estradiol benzoate | 130100601        | 1       |
| Alliance Healthcare        | Estradiol benzoate | 1301006-01       | 1       |
| Caelo                      | Estradiol benzoate | 13277602         | 9       |
| Noweda                     | Estradiol benzoate | 13277603         | 1       |
| Caelo                      | Estradiol benzoate | 13277603         | 2       |
| Fagron                     | Estradiol benzoate | 13C15-B07-288646 | 1       |
| Fagron                     | Estradiol benzoate | 13I11N01         | 1       |
| Fagron                     | Estradiol benzoate | 13I11-N01        | 1       |
| Caelo                      | Estradiol benzoate | 2021211-1        | 1       |
| Caelo                      | Estradiol benzoate | 21121204         | 1       |
| Fagron                     | Estradiol benzoate | 2x12L14-N02      | 1       |
| Fagron                     | Estradiol benzoate | 81403680         | 1       |
| Fagron                     | Estradiol benzoate | 81403690         | 1       |
| Fagron                     | Estradiol benzoate | 81403700         | 1       |
| Caelo                      | Estradiol benzoate | 81403700         | 1       |
| Caelo                      | Estradiol benzoate | 92137389         | 1       |
| VDL                        | Estradiol benzoate | 1507009-01       | 1       |
| Gehe                       | Estradiol benzoate | 10124913         | 1       |
| GEHE                       | Estradiol benzoate | 12B08-N05        | 1       |
| VDI 16.10.14 12,70 euro    | Estradiol benzoate |                  | 1       |
| Caelo                      | Estradiol benzoate | 1301006-02       | 1       |

- 69 372 spectra from 414 *Apo-Ident* customers from a total of 23 728 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Estradiol benzoate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Estradiol benzoate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 320           | 0              | 71 066        |
| <b>Type B</b> | 0              | 240           | 0              | 146 489       |
| <b>Type C</b> | 0              | 239           | 22             | 69 372        |

The substance/substance group *Estradiol benzoate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.1250 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 91.5709 % (> 90.4215 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20889     | 21290               | 3.94                         | 66.04                           |
| 21257     | 21290               | 1.01                         | 65.98                           |
| 21290     | 21290               | 0.00                         | 66.56                           |
| 21869     | 21869               | 0.00                         | 68.48                           |
| 23218     | 21869               | 9.91                         | 65.83                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Estradiol hemihydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20497-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Estradiol hemihydrate; Estradiolum hemihydricum; Oestradiolum hemihydricum

### Special notes

When selecting the *Estradiol hemihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Estradiol hemihydrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Estradiol hemihy... | 1208022-01       | 21291     | 40      | 20121012    |
| Caelo    | Estradiol hemihy... | 12268016         | 21302     | 40      | 1410502     |
| Caelo    | Estradiol hemihy... | 13285802         | 21508     | 40      | 1410504     |
| Fagron   | Estradiol hemihy... | 14G24-B04-297404 | 21667     | 40      | 20140825    |
| Euro OTC | Estradiol hemihy... | 1507013          | 21847     | 40      | 1510623     |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Estradiol hemihy... | 1510039          | 21945     | 40      | 20151103*   |
| Euro OTC | Estradiol hemihy... | 1601017          | 22307     | 30      | 20160122*   |
| Euro OTC | Estradiol hemihy... | 1612008          | 22913     | 40      | 20170117*   |
| Fagron   | Estradiol hemihy... | 16H04-B01-328738 | 23184     | 40      | 20160915    |
| Euro OTC | Estradiol hemihy... | 1507013          | 21847SI   | 40      | 1510623     |
| Euro OTC | Estradiol hemihy... | 1510039          | 21945SI   | 69      | 20151103*   |
| Euro OTC | Estradiol hemihy... | 1612008          | 22913SI   | 40      | 20170117*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 499 spectra of 12 reference samples from the substance/substance group *Estradiol hemihydrate*. These samples are listed above in the [calibration samples](#) section.
- 70 887 spectra from a total of 1543 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 1125 spectra of 38 reference samples from the substance/substance group *Estradiol hemihydrate*.

| Supplier | Substance             | Batch     | Sample ID | Spectra |
|----------|-----------------------|-----------|-----------|---------|
| Fagron   | Estradiol hemihydrate | 11H23-N02 | 20497     | 40      |
| Caelo    | Estradiol hemihydrate | 11078109  | 20503     | 40      |
| Fagron   | Estradiol hemihydrate | 13K22-N01 | 21263     | 40      |
| Caelo    | Estradiol hemihydrate | 13285802  | 21499     | 60      |
| Caelo    | Estradiol hemihydrate | 13285802  | 21500     | 60      |
| Caelo    | Estradiol hemihydrate | 13285802  | 21501     | 20      |
| Caelo    | Estradiol hemihydrate | 13285802  | 21502     | 20      |
| Caelo    | Estradiol hemihydrate | 13285802  | 21503     | 20      |
| Caelo    | Estradiol hemihydrate | 13285802  | 21504     | 20      |
| Caelo    | Estradiol hemihydrate | 13285802  | 21505     | 20      |
| Caelo    | Estradiol hemihydrate | 13285802  | 21506     | 20      |
| Caelo    | Estradiol hemihydrate | 13285802  | 21507     | 20      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

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| Supplier | Substance             | Batch            | Sample ID            | Spectra |
|----------|-----------------------|------------------|----------------------|---------|
| Caelo    | Estradiol hemihydrate | 13285802         | 21508 <sup>†</sup>   | 20      |
| Fagron   | Estradiol hemihydrate | 14G24-B04-297404 | 21667 <sup>†</sup>   | 15      |
| Euro OTC | Estradiol hemihydrate | 1507013          | 21847 <sup>†</sup>   | 20      |
| Euro OTC | Estradiol hemihydrate | 1510039          | 21945 <sup>†</sup>   | 20      |
| Euro OTC | Estradiol hemihydrate | 1601017          | 22307 <sup>†</sup>   | 15      |
| Euro OTC | Estradiol hemihydrate | 1607003          | 22712                | 40      |
| Euro OTC | Estradiol hemihydrate | 1612008-01       | 23099                | 40      |
| Caelo    | Estradiol hemihydrate | 170582           | 23339                | 40      |
| Euro OTC | Estradiol hemihydrate | 1705018          | 23431                | 30      |
| Caelo    | Estradiol hemihydrate | 13285802         | 21499SI              | 60      |
| Caelo    | Estradiol hemihydrate | 13285802         | 21500SI              | 60      |
| Caelo    | Estradiol hemihydrate | 13285802         | 21501SI              | 20      |
| Caelo    | Estradiol hemihydrate | 13285802         | 21502SI              | 20      |
| Caelo    | Estradiol hemihydrate | 13285802         | 21503SI              | 20      |
| Caelo    | Estradiol hemihydrate | 13285802         | 21504SI              | 20      |
| Caelo    | Estradiol hemihydrate | 13285802         | 21505SI              | 20      |
| Caelo    | Estradiol hemihydrate | 13285802         | 21506SI              | 20      |
| Caelo    | Estradiol hemihydrate | 13285802         | 21507SI              | 20      |
| Euro OTC | Estradiol hemihydrate | 1507013          | 21847SI <sup>†</sup> | 20      |
| Euro OTC | Estradiol hemihydrate | 1510039          | 21945SI <sup>†</sup> | 20      |
| Euro OTC | Estradiol hemihydrate | 1601017          | 22307SI              | 45      |
| Euro OTC | Estradiol hemihydrate | 1607003          | 22712SI              | 40      |
| Euro OTC | Estradiol hemihydrate | 1612008-01       | 23099SI              | 30      |
| Fagron   | Estradiol hemihydrate | 16H04-B01-328738 | 23184SI              | 30      |
| Caelo    | Estradiol hemihydrate | 170582           | 23339SI              | 30      |
| Euro OTC | Estradiol hemihydrate | 1705018          | 23431SI              | 30      |

- 145 604 spectra from a total of 3181 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 107 spectra from 67 *Apo-Ident* customers from 53 batches from the substance/substance group *Estradiol hemihydrate*.

| Supplier | Substance             | Batch      | Spectra |
|----------|-----------------------|------------|---------|
| Caelo    | Estradiol hemihydrate | 11078105   | 1       |
| Euro OTC | Estradiol hemihydrate | 120802201  | 1       |
| Caelo    | Estradiol hemihydrate | 12268012   | 5       |
| Fagron   | Estradiol hemihydrate | 12268011   | 2       |
| Euro OTC | Estradiol hemihydrate | 1308003-01 | 2       |
| Caelo    | Estradiol hemihydrate | 13285802   | 5       |
| phönix   | Estradiol hemihydrate | 13285802   | 1       |
| Caelo    | Estradiol hemihydrate | 13285811   | 3       |
| Fagron   | Estradiol hemihydrate | 13E07-N02  | 3       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier                   | Substance             | Batch            | Spectra |
|----------------------------|-----------------------|------------------|---------|
| Fagron                     | Estradiol hemihydrate | 13K22-N01        | 6       |
| Bayer Pharma               | Estradiol hemihydrate | 13K22-N01        | 2       |
| Fagron                     | Estradiol hemihydrate | 13K22N01         | 1       |
| Euro OTC                   | Estradiol hemihydrate | 1404030-01       | 1       |
| Euro OTC                   | Estradiol hemihydrate | 1411024-01       | 1       |
| Euro OTC                   | Estradiol hemihydrate | 14G24-B04-297402 | 1       |
| Fagron                     | Estradiol hemihydrate | 14G24-B04-297402 | 3       |
| Fagron                     | Estradiol hemihydrate | 14G24-B04-297404 | 2       |
| Fagron                     | Estradiol hemihydrate | 14G24-B04-297405 | 1       |
| Fagron                     | Estradiol hemihydrate | 14G24-B04-297406 | 1       |
| Fagron                     | Estradiol hemihydrate | 14G24-B04-302446 | 2       |
| Noweda                     | Estradiol hemihydrate | 15038004         | 1       |
| Caelo                      | Estradiol hemihydrate | 15038004         | 7       |
| Caelo                      | Estradiol hemihydrate | 15038010         | 2       |
| Caelo                      | Estradiol hemihydrate | 1503801          | 1       |
| Caelo                      | Estradiol hemihydrate | 15038014         | 2       |
| Gehe                       | Estradiol hemihydrate | 15038016         | 1       |
| Euro OTC                   | Estradiol hemihydrate | 1510039-01       | 1       |
| Euro OTC                   | Estradiol hemihydrate | 15D01-B02        | 1       |
| Fagron                     | Estradiol hemihydrate | 15D01-B02-308190 | 1       |
| Fagron                     | Estradiol hemihydrate | 15D01-B02-308568 | 1       |
| Fagron                     | Estradiol hemihydrate | 15D01-B02-319032 | 2       |
| Caelo                      | Estradiol hemihydrate | 15D01-B02-319032 | 1       |
| Euro OTC                   | Estradiol hemihydrate | 1601017-01       | 1       |
| Caelo                      | Estradiol hemihydrate | 160700301        | 1       |
| Caelo                      | Estradiol hemihydrate | 19051501         | 1       |
| Caelo                      | Estradiol hemihydrate | 2/AKD13          | 1       |
| Fagron                     | Estradiol hemihydrate | 302446           | 1       |
| Fagron                     | Estradiol hemihydrate | 83100820         | 2       |
| Fagron                     | Estradiol hemihydrate | 84201170         | 1       |
| Caelo                      | Estradiol hemihydrate | 84201560         | 1       |
| Caelo                      | Estradiol hemihydrate | 9248916          | 3       |
| Alliance Health 27.05.2... | Estradiol hemihydrate | 9A09-N26         | 1       |
| Fagron                     | Estradiol hemihydrate | 9J27-N05         | 1       |
| Fagron                     | Estradiol hemihydrate | 11031401         | 1       |
| Caelo                      | Estradiol hemihydrate | 11078104         | 1       |
| Caelo                      | Estradiol hemihydrate | 12172003         | 2       |
| Caelo                      | Estradiol hemihydrate | 11078113         | 1       |
| Fagron                     | Estradiol hemihydrate | 11H23-N02        | 1       |
| Caelo                      | Estradiol hemihydrate | 12268003         | 2       |
| Noweda                     | Estradiol hemihydrate | 12268008         | 1       |
| Fagron                     | Estradiol hemihydrate | 12F29-N03        | 6       |
| Fagron                     | Estradiol hemihydrate | 12F29-N03        | 1       |
| Fagron                     | Estradiol hemihydrate | 12L19-N07        | 6       |
| Fagron                     | Estradiol hemihydrate | 12L29-N07        | 1       |
| Caelo                      | Estradiol hemihydrate | 13285801         | 1       |
| Caelo                      | Estradiol hemihydrate | 22101301         | 1       |
| Gehe                       | Estradiol hemihydrate | 82404160         | 1       |
| Euro OTC                   | Estradiol hemihydrate | 1607003-01       | 1       |
| Caelo                      | Estradiol hemihydrate | 12F29-N03        | 1       |

- 69 526 spectra from 414 *Apo-Ident* customers from a total of 23 748 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).



## Validation results

The validation runs checked whether the substance/substance group *Estradiol hemihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Estradiol hemihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 498           | 1              | 70 887        |
| <b>Type B</b> | 0              | 1125          | 0              | 145 604       |
| <b>Type C</b> | 0              | 104           | 3              | 69 526        |

The substance/substance group *Estradiol hemihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 99.7996 % (> 99.1984 %)  |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 99.4667 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 97.1963 % (> 94.3925 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21291     | 21945               | 3.20                         | 37.04                           |
| 21302     | 21302               | 0.00                         | 34.66                           |
| 21508     | 21508               | 0.00                         | 38.85                           |
| 21667     | 21945               | 1.55                         | 36.81                           |
| 21847     | 21847               | 0.00                         | 43.83                           |
| 21945     | 21945               | 0.00                         | 38.03                           |
| 22307     | 22307               | 0.00                         | 37.65                           |
| 22913     | 22913               | 0.00                         | 36.13                           |
| 23184     | 21945               | 2.98                         | 36.63                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Estradiol valerate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20330-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Estradiol valerate; Estradioli valeras; Oestradiolum valerianicum

### Special notes

When selecting the *Estradiol valerate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Estradiol valerate*:

| Supplier | Substance          | Batch     | Sample ID | Spectra | Certificate |
|----------|--------------------|-----------|-----------|---------|-------------|
| Fagron   | Estradiol valerate | 12D18-N02 | 20651     | 40      | 20120426    |
| Fagron   | Estradiol valerate | 12D18-N02 | 21266     | 40      | 20120118    |
| Caelo    | Estradiol valerate | 13264001  | 21411     | 40      | 1410503     |
| Caelo    | Estradiol valerate | 13264001  | 21416     | 60      | 1510624     |
| Caelo    | Estradiol valerate | 13264001  | 21424     | 40      | 1410503     |

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| Supplier | Substance          | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------------|------------------|-----------|---------|-------------|
| Fagron   | Estradiol valerate | 14E26-B02-294846 | 21646     | 40      | 20140616    |
| Caelo    | Estradiol valerate | 15194802         | 21989     | 40      | 20150708    |
| Caelo    | Estradiol valerate | 163277           | 23056     | 40      | 20161221*   |
| Caelo    | Estradiol valerate | 13264001         | 21411SI   | 30      | 1410503     |
| Caelo    | Estradiol valerate | 13264001         | 21416SI   | 30      | 1510624     |
| Caelo    | Estradiol valerate | 15194802         | 21989SI   | 20      | 20150708    |
| Caelo    | Estradiol valerate | 163277           | 23056SI   | 40      | 20161221*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 460 spectra of 12 reference samples from the substance/substance group *Estradiol valerate*. These samples are listed above in the [calibration samples](#) section.
- 70926 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 467 spectra of 23 reference samples from the substance/substance group *Estradiol valerate*.

| Supplier | Substance          | Batch            | Sample ID          | Spectra |
|----------|--------------------|------------------|--------------------|---------|
| Fagron   | Estradiol valerate | 11G18-N04        | 20330              | 40      |
| Caelo    | Estradiol valerate | 13264001         | 21411 <sup>†</sup> | 20      |
| Caelo    | Estradiol valerate | 13264001         | 21416 <sup>†</sup> | 60      |
| Caelo    | Estradiol valerate | 13264001         | 21417              | 20      |
| Caelo    | Estradiol valerate | 13264001         | 21418              | 20      |
| Caelo    | Estradiol valerate | 13264001         | 21419              | 20      |
| Caelo    | Estradiol valerate | 13264001         | 21422              | 20      |
| Caelo    | Estradiol valerate | 13264001         | 21423              | 20      |
| Caelo    | Estradiol valerate | 13264001         | 21424 <sup>†</sup> | 20      |
| Caelo    | Estradiol valerate | 13264001         | 21425              | 20      |
| Caelo    | Estradiol valerate | 13264001         | 21426              | 20      |
| Fagron   | Estradiol valerate | 14E26-B02-294846 | 21646 <sup>†</sup> | 20      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

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| Supplier | Substance          | Batch    | Sample ID            | Spectra |
|----------|--------------------|----------|----------------------|---------|
| Caelo    | Estradiol valerate | 15194802 | 21989 <sup>†</sup>   | 20      |
| Caelo    | Estradiol valerate | 13264001 | 21411SI <sup>†</sup> | 15      |
| Caelo    | Estradiol valerate | 13264001 | 21416SI <sup>†</sup> | 15      |
| Caelo    | Estradiol valerate | 13264001 | 21417SI              | 14      |
| Caelo    | Estradiol valerate | 13264001 | 21418SI              | 15      |
| Caelo    | Estradiol valerate | 13264001 | 21419SI              | 15      |
| Caelo    | Estradiol valerate | 13264001 | 21422SI              | 17      |
| Caelo    | Estradiol valerate | 13264001 | 21423SI              | 15      |
| Caelo    | Estradiol valerate | 13264001 | 21425SI              | 15      |
| Caelo    | Estradiol valerate | 13264001 | 21426SI              | 16      |
| Caelo    | Estradiol valerate | 15194802 | 21989SI <sup>†</sup> | 10      |

- 146 262 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 97 spectra from 50 *Apo-Ident* customers from 48 batches from the substance/substance group *Estradiol valerate*.

| Supplier        | Substance          | Batch            | Spectra |
|-----------------|--------------------|------------------|---------|
| Fagron          | Estradiol valerate | 13g09-n05        | 2       |
| Fagron          | Estradiol valerate | 12A20-N10        | 3       |
| Fagron          | Estradiol valerate | 814M-03259       | 1       |
| Caelo           | Estradiol valerate | 13264001         | 1       |
| Fagron          | Estradiol valerate | 13A07-N11        | 6       |
| Fagron          | Estradiol valerate | 13D16-N10        | 4       |
| Fagron          | Estradiol valerate | 13G09N05         | 1       |
| Fagron          | Estradiol valerate | 13G09-N05        | 5       |
| Fagron          | Estradiol valerate | 13I13-N02        | 2       |
| Fagron          | Estradiol valerate | 14E26B02         | 2       |
| Fagron          | Estradiol valerate | 14E26-B02-294844 | 1       |
| Fagron          | Estradiol valerate | 14E26-B02-294845 | 3       |
| Caelo           | Estradiol valerate | 14E26-B02-294845 | 1       |
| Fagron          | Estradiol valerate | 14E26-B02-294847 | 1       |
| Fagron          | Estradiol valerate | 14E26-B02-296348 | 4       |
| Fagron          | Estradiol valerate | 14E26-b02-302872 | 1       |
| Fagron          | Estradiol valerate | 14E26-B02-302873 | 2       |
| Fagron          | Estradiol valerate | 15C10-B05        | 1       |
| Fagron          | Estradiol valerate | 15C10-B05-305395 | 3       |
| Bayer Pharma AG | Estradiol valerate | 15C10-B05-305395 | 1       |
| Caelo           | Estradiol valerate | 15c10-B05-305396 | 1       |
| Fagron          | Estradiol valerate | 15C10-B05-308851 | 6       |
| Caelo           | Estradiol valerate | 15C10B05308851   | 1       |
| Fagron          | Estradiol valerate | 15c10-b05-309186 | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier          | Substance          | Batch            | Spectra |
|-------------------|--------------------|------------------|---------|
| Fagron            | Estradiol valerate | 15C10-B05-313568 | 1       |
| Fagron            | Estradiol valerate | 15C10-B05-314840 | 3       |
| Fagron            | Estradiol valerate | 15C10B05321675   | 1       |
| Fagron            | Estradiol valerate | 15C10-B05-321675 | 2       |
| Phönix            | Estradiol valerate | 15C10-B05-326087 | 1       |
| Fagron            | Estradiol valerate | 15C10-B05-326087 | 1       |
| Fagron            | Estradiol valerate | 15C10B05-326087  | 1       |
| Fagron            | Estradiol valerate | 19c10-b05-318405 | 1       |
| Fagron            | Estradiol valerate | 24052014a        | 1       |
| Caelo             | Estradiol valerate | 4214U-03259      | 1       |
| Caelo             | Estradiol valerate | 5315A-03259      | 1       |
| Fagron            | Estradiol valerate | 10L20-N05        | 1       |
| Fagron            | Estradiol valerate | 11G18-N04        | 1       |
| Fagron            | Estradiol valerate | 11J13-N09        | 1       |
| Fagron            | Estradiol valerate | 11J13-No9        | 1       |
| Fagron            | Estradiol valerate | 11K04-N04        | 1       |
| Fagron            | Estradiol valerate | 11k04-n04        | 1       |
| Noweda            | Estradiol valerate | 12A20-N10        | 1       |
| Fagron            | Estradiol valerate | 12D18-N02        | 3       |
| Caelo             | Estradiol valerate | 12G05-N09        | 2       |
| Fagron            | Estradiol valerate | 12G05-N09        | 1       |
| Fagron            | Estradiol valerate | 12G05N09         | 1       |
| Fagron            | Estradiol valerate | 12K05-N02        | 2       |
| Sanacorp          | Estradiol valerate | 13264002         | 1       |
| Caelo             | Estradiol valerate | 13264002         | 1       |
| Caelo             | Estradiol valerate | 13264003         | 1       |
| Jenne             | Estradiol valerate | 13A07-N11        | 1       |
| Fagron            | Estradiol valerate | 13a07-n11        | 1       |
| Fagron            | Estradiol valerate | 13D16N10         | 1       |
| Phoenix           | Estradiol valerate | 13G09-N05        | 1       |
| Fagron            | Estradiol valerate | 82201620         | 1       |
| Bayer Pharma GmbH | Estradiol valerate | 82201620         | 1       |
| Caelo             | Estradiol valerate | test             | 1       |
| Beiersdorf/AHD    | Estradiol valerate | 12A20-N10        | 1       |
| Beiersdorf/AHD    | Estradiol valerate | 12G05-N09        | 2       |

- 69 536 spectra from 414 *Apo-Ident* customers from a total of 23 754 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Estradiol valerate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Estradiol valerate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 460           | 0              | 70 926        |
| <b>Type B</b> | 0              | 467           | 0              | 146 262       |
| <b>Type C</b> | 0              | 95            | 2              | 69 536        |

The substance/substance group *Estradiol valerate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.6957 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.7152 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 97.9381 % (> 94.8454 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 20651            | 21416                      | 2.27                                | 39.93                                  |
| 21266            | 23056                      | 4.73                                | 52.80                                  |
| 21411            | 21411                      | 0.00                                | 38.05                                  |
| 21416            | 21416                      | 0.00                                | 39.14                                  |
| 21424            | 21424                      | 0.00                                | 45.97                                  |
| 21646            | 21424                      | 5.93                                | 51.19                                  |
| 21989            | 21424                      | 2.70                                | 44.67                                  |
| 23056            | 23056                      | 0.00                                | 55.20                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Estriol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20878-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Estriol; Estriolum; Oestriolum

### Special notes

When selecting the *Estriol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Estriol*:

| Supplier | Substance | Batch     | Sample ID | Spectra | Certificate |
|----------|-----------|-----------|-----------|---------|-------------|
| Caelo    | Estriol   | 12298706  | 20878     | 40      | 20121106    |
| Fagron   | Estriol   | 11J13-N07 | 21255     | 40      | 1412180     |
| Caelo    | Estriol   | 13256001  | 21390     | 50      | 1511155     |
| Euro OTC | Estriol   | 1507026   | 21848     | 40      | 0000010671  |
| Euro OTC | Estriol   | 1509042   | 21939     | 40      | 20151009*   |

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| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Fagron   | Estriol   | 16D15-B03-322957 | 22889     | 40      | 20160711    |
| Fagron   | Estriol   | 16I19-B01-331468 | 23172     | 40      | 20170301    |
| Euro OTC | Estriol   | 1703044          | 23181     | 40      | 20170502*   |
| Caelo    | Estriol   | 13256001         | 21390SI   | 40      | 1511155     |
| Euro OTC | Estriol   | 1507026          | 21848SI   | 40      | 0000010671  |
| Euro OTC | Estriol   | 1509042          | 21939SI   | 40      | 20151009*   |
| Fagron   | Estriol   | 16D15-B03-322957 | 22889SI   | 40      | 20160711    |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 490 spectra of 12 reference samples from the substance/substance group *Estriol*. These samples are listed above in the *calibration samples* section.
- 70 896 spectra from a total of 1544 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this *chemometric model*, the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in *Appendix A*. The samples in *Appendix A* were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 910 spectra of 32 reference samples from the substance/substance group *Estriol*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Euro OTC | Estriol   | 1310002-01 | 21292              | 40      |
| Caelo    | Estriol   | 13256001   | 21390 <sup>†</sup> | 20      |
| Caelo    | Estriol   | 13256001   | 21391              | 60      |
| Caelo    | Estriol   | 13256001   | 21392              | 20      |
| Caelo    | Estriol   | 13256001   | 21393              | 60      |
| Caelo    | Estriol   | 13256001   | 21394              | 20      |
| Caelo    | Estriol   | 13256001   | 21395              | 15      |
| Caelo    | Estriol   | 13256001   | 21399              | 15      |
| Caelo    | Estriol   | 13256001   | 21400              | 20      |
| Caelo    | Estriol   | 13256001   | 21401              | 20      |
| Caelo    | Estriol   | 13256001   | 21404              | 20      |
| Euro OTC | Estriol   | 1507026    | 21848 <sup>†</sup> | 20      |
| Euro OTC | Estriol   | 1509042    | 21939 <sup>†</sup> | 20      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

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| Supplier | Substance | Batch            | Sample ID            | Spectra |
|----------|-----------|------------------|----------------------|---------|
| Caelo    | Estriol   | 161382           | 22633                | 40      |
| Euro OTC | Estriol   | 1606044          | 22711                | 40      |
| Euro OTC | Estriol   | 1610035          | 22850                | 40      |
| Caelo    | Estriol   | 13256001         | 21390SI <sup>†</sup> | 20      |
| Caelo    | Estriol   | 13256001         | 21391SI              | 60      |
| Caelo    | Estriol   | 13256001         | 21392SI              | 20      |
| Caelo    | Estriol   | 13256001         | 21394SI              | 20      |
| Caelo    | Estriol   | 13256001         | 21395SI              | 15      |
| Caelo    | Estriol   | 13256001         | 21399SI              | 15      |
| Caelo    | Estriol   | 13256001         | 21400SI              | 20      |
| Caelo    | Estriol   | 13256001         | 21401SI              | 20      |
| Caelo    | Estriol   | 13256001         | 21404SI              | 20      |
| Euro OTC | Estriol   | 1507026          | 21848SI <sup>†</sup> | 20      |
| Euro OTC | Estriol   | 1509042          | 21939SI <sup>†</sup> | 20      |
| Caelo    | Estriol   | 161382           | 22633SI              | 40      |
| Euro OTC | Estriol   | 1606044          | 22711SI              | 40      |
| Euro OTC | Estriol   | 1610035          | 22850SI              | 40      |
| Fagron   | Estriol   | 16I19-B01-331468 | 23172SI              | 30      |
| Euro OTC | Estriol   | 1703044          | 23181SI              | 40      |

- 145819 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 173 spectra from 81 *Apo-Ident* customers from 79 batches from the substance/substance group *Estriol*.

| Supplier | Substance | Batch      | Spectra |
|----------|-----------|------------|---------|
| Caelo    | Estriol   | 10053206   | 1       |
| Caelo    | Estriol   | 10H30-N06  | 1       |
| Caelo    | Estriol   | 11254402   | 2       |
| Noweda   | Estriol   | 11254409   | 1       |
| Caelo    | Estriol   | 11254408   | 1       |
| Caelo    | Estriol   | 11254410   | 1       |
| Caelo    | Estriol   | 11254412   | 2       |
| Fagron   | Estriol   | 11D13-N11  | 1       |
| Fagron   | Estriol   | 11J13-N07  | 3       |
| Noweda   | Estriol   | 11J13-No7  | 1       |
| Euro OTC | Estriol   | 1201020-01 | 1       |
| Caelo    | Estriol   | 12032503   | 4       |
| Noweda   | Estriol   | 12032504   | 1       |
| Caelo    | Estriol   | 12032504   | 2       |
| Caelo    | Estriol   | 12032507   | 5       |
| Caelo    | Estriol   | 12298702   | 2       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------|------------------|----------------|
| Caelo                      | Estriol          | 12298704         | 7              |
| Caelo                      | Estriol          | 12298706         | 3              |
| Caelo                      | Estriol          | 12298707         | 3              |
| Caesar § Lorenz GmbH       | Estriol          | 12298712         | 1              |
| Fagron                     | Estriol          | 12A26-N02        | 2              |
| Fagron                     | Estriol          | 12F08-N06        | 1              |
| Caelo                      | Estriol          | 12H06N02         | 1              |
| Caelo                      | Estriol          | 12H06-N02        | 2              |
| Fagron                     | Estriol          | 12H06-N02        | 5              |
| Fagron                     | Estriol          | 12H06-No2        | 2              |
| Fagron                     | Estriol          | 12K07-N15        | 2              |
| Euro OTC                   | Estriol          | 1310002-01       | 1              |
| Caelo                      | Estriol          | 13256004         | 9              |
| VDL                        | Estriol          | 13256004         | 1              |
| Sanacorp                   | Estriol          | 13256004         | 1              |
| Caelo                      | Estriol          | 1356001          | 1              |
| Fagron                     | Estriol          | 13C15-N04        | 4              |
| Fagron                     | Estriol          | 13D19-N02        | 1              |
| Sanacorp                   | Estriol          | 13D19-N05        | 1              |
| Fagron                     | Estriol          | 13H28-N01        | 4              |
| Euro OTC                   | Estriol          | 1403011-01       | 3              |
| Caelo                      | Estriol          | 14077901         | 1              |
| Caelo                      | Estriol          | 14077903         | 3              |
| Caelo                      | Estriol          | 14077904         | 8              |
| Kehr/Apomix                | Estriol          | 14077904         | 1              |
| Euro OTC                   | Estriol          | 1409018-01       | 2              |
| Caelo                      | Estriol          | 1409018-01       | 1              |
| Caelo                      | Estriol          | 14272101         | 3              |
| Caelo                      | Estriol          | 14272104         | 3              |
| Noweda 19.05.2015          | Estriol          | 14272104         | 1              |
| Caelo                      | Estriol          | 1477904          | 1              |
| Fagron                     | Estriol          | 14B06-B11-291563 | 1              |
| Gehe 30.12.14              | Estriol          | 14B06-B11-291563 | 1              |
| Fagron                     | Estriol          | 14B06-B11-291565 | 1              |
| Fagron                     | Estriol          | 14B06-B11-294565 | 1              |
| Fagron                     | Estriol          | 14E13-B01        | 2              |
| Fagron                     | Estriol          | 14E13-B01-294034 | 4              |
| Fagron                     | Estriol          | 14E29-B02        | 1              |
| Fischar/Gehe               | Estriol          | 14H29-B02-298072 | 3              |
| Fagron                     | Estriol          | 14H29-B02-298074 | 2              |
| Caelo                      | Estriol          | 15008902         | 1              |
| Caelo                      | Estriol          | 15028901         | 1              |
| Caesar & Loretz GmbH       | Estriol          | 15028901         | 1              |
| Euro OTC                   | Estriol          | 15028904         | 1              |
| Caesar & Loretz GmbH       | Estriol          | 15028904         | 1              |
| Caelo                      | Estriol          | 15028904         | 1              |
| Caelo                      | Estriol          | 15028905         | 2              |
| Caesar&Loretz,AHC, 19.0... | Estriol          | 15297804         | 1              |
| Caelo                      | Estriol          | 15297804         | 6              |
| Fagron                     | Estriol          | 15297804         | 2              |
| Fagron                     | Estriol          | 15A15-B07-312064 | 1              |
| Caelo                      | Estriol          | 15297805         | 1              |
| Ensbona/ Sanacorp          | Estriol          | 16053405         | 1              |
| Caelo                      | Estriol          | 16053405         | 2              |
| Gehe                       | Estriol          | 16053405         | 1              |
| Euro OTC                   | Estriol          | 1610035-01       | 1              |
| Sanacorp                   | Estriol          | 16317701         | 1              |
| Caelo                      | Estriol          | 16053408         | 1              |
| Euro OTC                   | Estriol          | 1606044-01       | 1              |
| Sanacorp                   | Estriol          | 16317702         | 1              |

*continued on the next page*

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| Supplier                   | Substance | Batch         | Spectra |
|----------------------------|-----------|---------------|---------|
| Caelo                      | Estriol   | 16317703      | 2       |
| Caelo                      | Estriol   | 17042014B     | 1       |
| Caelo                      | Estriol   | 24031501      | 1       |
| Haihang Industry           | Estriol   | 20130824      | 1       |
| Caelo                      | Estriol   | 27061303      | 1       |
| Fagron                     | Estriol   | 81100490      | 1       |
| Caelo                      | Estriol   | 20040711-9    | 1       |
| Bombastus                  | Estriol   | 5128          | 1       |
| Audor Pharma               | Estriol   | APL000036940E | 1       |
| Audor Pharma               | Estriol   | APL00036940E  | 2       |
| Audor Pharma               | Estriol   | APL00037293E  | 1       |
| Audor Pharma               | Estriol   |               | 1       |
| NWM CHina                  | Estriol   | ES150304      | 1       |
| Shandong Northwest Manu... | Estriol   | ETL160302     | 1       |
| Shandong Northwest Manu... | Estriol   | ETL160419     | 1       |
| fargon                     | Estriol   | 12a26-n02     | 1       |
| Caelo                      | Estriol   | 16138204      | 1       |
| Caelo                      | Estriol   | 16317702      | 1       |
| Caelo                      | Estriol   | 13256001      | 1       |

- 69 460 spectra from 414 *Apo-Ident* customers from a total of 23 723 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Estriol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Estriol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 490           | 0              | 70 896        |
| <b>Type B</b> | 0              | 905           | 5              | 145 819       |
| <b>Type C</b> | 0              | 166           | 7              | 69 460        |

The substance/substance group *Estriol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.7755 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.4505 % (> 99.1209 %)  |
| <b>Type C</b> | 100.0000 % (> 99.9813 %) | 95.9538 % (> 94.2197 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to

exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20878     | 21939               | 3.12                         | 42.08                           |
| 21255     | 21255               | 0.00                         | 43.40                           |
| 21390     | 21390               | 0.00                         | 29.94                           |
| 21848     | 21848               | 0.00                         | 30.73                           |
| 21939     | 21939               | 0.00                         | 38.10                           |
| 22889     | 23181               | 7.60                         | 49.76                           |
| 23172     | 21939               | 3.80                         | 42.11                           |
| 23181     | 23181               | 0.00                         | 48.85                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Ethacridine lactate monohydrate</b>                          |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20750-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Ethacridine lactate monohydrate; Aethacridinum lacticum monohydricum; Ethacridini lactas monohydricus

### Special notes

When selecting the *Ethacridine lactate monohydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ethacridine lactate monohydrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Caelo    | Ethacridine lact... | 12149507         | 20750     | 40      | 20120619           |
| Fagron   | Ethacridine lact... | 13I24-N03        | 21265     | 40      | AR-15-FG-007011-02 |
| Euro OTC | Ethacridine lact... | 1206016-02       | 21636     | 40      | 20121019           |
| Fagron   | Ethacridine lact... | 15A29-B02-306219 | 22500     | 40      | 20150205           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Ethacridine lactate monohydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Ethacridine lactate monohydrate*.

| Supplier | Substance                       | Batch      | Sample ID          | Spectra |
|----------|---------------------------------|------------|--------------------|---------|
| Euro OTC | Ethacridine lactate monohydr... | 1206016-02 | 21636 <sup>†</sup> | 20      |
| Euro OTC | Ethacridine lactate monohydr... | 1412034-02 | 22733              | 40      |
| Caelo    | Ethacridine lactate monohydr... | 16273403   | 23247              | 40      |
| Caelo    | Ethacridine lactate monohydr... | 172476     | 23671              | 40      |

- 146 589 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 125 spectra from 80 *Apo-Ident* customers from 45 batches from the substance/substance group *Ethacridine lactate monohydrate*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier                   | Substance                       | Batch            | Spectra |
|----------------------------|---------------------------------|------------------|---------|
| Chinosol/Anzag             | Ethacridine lactate monohydr... | 914E-02196       | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 14A15-B04-300493 | 7       |
| Fagron                     | Ethacridine lactate monohydr... | 12/24-N04        | 2       |
| Euro OTC                   | Ethacridine lactate monohydr... | 1206016-02       | 5       |
| Euro OTC                   | Ethacridine lactate monohydr... | 1206016-03       | 6       |
| Caelo                      | Ethacridine lactate monohydr... | 12268407         | 3       |
| Fagron                     | Ethacridine lactate monohydr... | 12G02-N13        | 7       |
| Euro OTC                   | Ethacridine lactate monohydr... | 13/24-N03        | 1       |
| Bombastus                  | Ethacridine lactate monohydr... | 13/24-N03        | 1       |
| phoenix 18.11.2014         | Ethacridine lactate monohydr... | 13/24-N03        | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 13/24-N03        | 2       |
| Fagron                     | Ethacridine lactate monohydr... | 13/24-N03        | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 13I24-N03        | 7       |
| Fagron                     | Ethacridine lactate monohydr... | 13I24-N03        | 1       |
| Caelo                      | Ethacridine lactate monohydr... | 141203401        | 1       |
| Euro OTC                   | Ethacridine lactate monohydr... | 1412034-01       | 3       |
| Caelo                      | Ethacridine lactate monohydr... | 1412034-01       | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 14A15-B04        | 1       |
| Caelo                      | Ethacridine lactate monohydr... | 15177603         | 3       |
| Caelo                      | Ethacridine lactate monohydr... | 15438003         | 3       |
| Caelo                      | Ethacridine lactate monohydr... | 15438007         | 3       |
| Euro OTC                   | Ethacridine lactate monohydr... | 15438007         | 1       |
| Caesar & Loretz GmbH Hi... | Ethacridine lactate monohydr... | 15438007         | 1       |
| Caelo                      | Ethacridine lactate monohydr... | 16272408         | 1       |
| Caelo                      | Ethacridine lactate monohydr... | 16273403         | 2       |
| Caelo                      | Ethacridine lactate monohydr... | 16273411         | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 16e20-b11-322514 | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 16E20-B11-322514 | 2       |
| Euro OTC                   | Ethacridine lactate monohydr... | 2905007v-03      | 1       |
| Dermapharm                 | Ethacridine lactate monohydr... | 100201           | 2       |
| Fagron                     | Ethacridine lactate monohydr... | 11/07-N05        | 1       |
| Caelo                      | Ethacridine lactate monohydr... | 10288702         | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 103485-0006      | 1       |
| Caelo                      | Ethacridine lactate monohydr... | 11173703         | 1       |
| Fargon                     | Ethacridine lactate monohydr... | 11D07-N03        | 1       |
| Caelo                      | Ethacridine lactate monohydr... | 11J07-N05        | 1       |
| Caelo                      | Ethacridine lactate monohydr... | 1206016-03       | 1       |
| Caelo                      | Ethacridine lactate monohydr... | 12149507         | 3       |
| Fagron                     | Ethacridine lactate monohydr... | 12C30-N07        | 2       |
| Caelo                      | Ethacridine lactate monohydr... | 12G02-N13        | 2       |
| Gehe                       | Ethacridine lactate monohydr... | 12G02-N13        | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 12G02-N135-15    | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 12J24-N04        | 1       |
| Phonix                     | Ethacridine lactate monohydr... | 13I24-N03        | 1       |
| Gehe                       | Ethacridine lactate monohydr... | 13I24-N03        | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 201205001        | 4       |
| Chinosol/Anzag             | Ethacridine lactate monohydr... | 2112A-02196      | 1       |
| Fagron                     | Ethacridine lactate monohydr... | 2405210013       | 1       |
| Euro OTC                   | Ethacridine lactate monohydr... | 2905007-01       | 2       |
| Euro OTC                   | Ethacridine lactate monohydr... | 2905007V-03      | 2       |
| Dermapharm                 | Ethacridine lactate monohydr... | 130201           | 6       |
| Dermapharm                 | Ethacridine lactate monohydr... | 141101           | 1       |
| Ebert & Jacobi 19.07...    | Ethacridine lactate monohydr... | 141101           | 2       |
| Dermopharm                 | Ethacridine lactate monohydr... | 141101           | 1       |
| Caelo                      | Ethacridine lactate monohydr... | 15/214/R         | 1       |
| Finze                      | Ethacridine lactate monohydr... | 90601            | 1       |
| Dermapharm                 | Ethacridine lactate monohydr... | 111201           | 7       |
| Phoenix                    | Ethacridine lactate monohydr... | 100201           | 1       |
| Anzag                      | Ethacridine lactate monohydr... | 111201           | 1       |
| Phönix                     | Ethacridine lactate monohydr... | 111201           | 1       |

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| Supplier   | Substance                         | Batch    | Spectra |
|------------|-----------------------------------|----------|---------|
| Caelo      | Ethacridine lactate monohydr. ... | 12149514 | 1       |
| Dermopharm | Ethacridine lactate monohydr. ... | 130201   | 1       |

- 69 508 spectra from 414 *Apo-Ident* customers from a total of 23 756 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ethacridine lactate monohydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ethacridine lactate monohydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 160           | 0              | 71 226        |
| Type B | 0              | 107           | 33             | 146 589       |
| Type C | 0              | 99            | 26             | 69 508        |

The substance/substance group *Ethacridine lactate monohydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| Type B | 100.0000 % (> 99.9923 %) | 76.4286 % (> 74.2857 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 79.2000 % (> 76.8000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20750     | 21265               | 11.74                        | 30.09                           |
| 21265     | 21265               | 0.00                         | 29.87                           |
| 21636     | 21265               | 7.67                         | 29.93                           |
| 22500     | 21265               | 13.10                        | 28.81                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ethinyl estradiol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20950-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ethinyl estradiol; Aethinyloestradiolum; Ethinyloestradiolum

### Special notes

When selecting the *Ethinyl estradiol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ethinyl estradiol*:

| Supplier | Substance         | Batch            | Sample ID | Spectra | Certificate |
|----------|-------------------|------------------|-----------|---------|-------------|
| Fagron   | Ethinyl estradiol | 13I09-N04        | 20950     | 40      | 1402058     |
| Fagron   | Ethinyl estradiol | 14E15-B03-296049 | 21705     | 40      | 1507109     |
| Fagron   | Ethinyl estradiol | 14E15-B03-310270 | 21916     | 40      | 20140708    |
| Fagron   | Ethinyl estradiol | 14E15-B03-296049 | 21705SI   | 36      | 1507109     |
| Fagron   | Ethinyl estradiol | 14E15-B03-310270 | 21916SI   | 40      | 20140708    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 196 spectra of 5 reference samples from the substance/substance group *Ethinyl estradiol*. These samples are listed above in the [calibration samples](#) section.
- 71 190 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 248 spectra of 8 reference samples from the substance/substance group *Ethinyl estradiol*.

| Supplier | Substance         | Batch            | Sample ID            | Spectra |
|----------|-------------------|------------------|----------------------|---------|
| Fagron   | Ethinyl estradiol | 14E15-B03-296049 | 21705 <sup>†</sup>   | 15      |
| Fagron   | Ethinyl estradiol | 14E15-B03-310270 | 21916 <sup>†</sup>   | 20      |
| Fagron   | Ethinyl estradiol | 14E15-B03-310270 | 21958                | 60      |
| Fagron   | Ethinyl estradiol | 16B17-B01-329904 | 23075                | 40      |
| Fagron   | Ethinyl estradiol | 14E15-B03-296049 | 21705SI <sup>†</sup> | 20      |
| Fagron   | Ethinyl estradiol | 14E15-B03-310270 | 21916SI <sup>†</sup> | 20      |
| Fagron   | Ethinyl estradiol | 14E15-B03-310270 | 21958SI              | 43      |
| Fagron   | Ethinyl estradiol | 16B17-B01-329904 | 23075SI              | 30      |

- 146 481 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 8 spectra from 7 *Apo-Ident* customers from 7 batches from the substance/substance group *Ethinyl estradiol*.

| Supplier | Substance         | Batch          | Spectra |
|----------|-------------------|----------------|---------|
| Fagron   | Ethinyl estradiol | 13G03-N04      | 1       |
| Caelo    | Ethinyl estradiol | 130909         | 1       |
| Fagron   | Ethinyl estradiol | 13I09-N04      | 1       |
| Fagron   | Ethinyl estradiol | 14e15b03296049 | 1       |
| Fagron   | Ethinyl estradiol | 16B17-B01      | 1       |
| Fagron   | Ethinyl estradiol | 84100720       | 1       |
| Fagron   | Ethinyl estradiol | 12D19-N04      | 2       |

- 69 625 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ethinyl estradiol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ethinyl estradiol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 196           | 0              | 71 190        |
| <b>Type B</b> | 0              | 248           | 0              | 146 481       |
| <b>Type C</b> | 0              | 6             | 2              | 69 625        |

The substance/substance group *Ethinyl estradiol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.9388 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5806 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20950     | 20950               | 0.00                         | 28.04                           |
| 21705     | 21705               | 0.00                         | 21.73                           |
| 21916     | 21705               | 9.69                         | 17.92                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ethyl hydrogen fumarate calcium**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21532-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ethyl hydrogen fumarate calcium; Calcii ethylhydrogenfumaras; Calcii ethylhydrogenofumaras

### Special notes

When selecting the *Ethyl hydrogen fumarate calcium* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ethyl hydrogen fumarate calcium*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Fagron   | Ethyl hydrogen f... | 13B25-N08  | 21532     | 40      | 1411090     |
| Euro OTC | Ethyl hydrogen f... | 1310029-01 | 21562     | 40      | 20131126    |
| Euro OTC | Ethyl hydrogen f... | 1306012-01 | 21641     | 40      | 1505456     |
| Euro OTC | Ethyl hydrogen f... | 1510005    | 21938     | 40      | 20151030*   |
| Euro OTC | Ethyl hydrogen f... | 1601011    | 22294     | 40      | 20160114*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Ethyl hydrogen fumarate calcium*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 112 spectra of 6 reference samples from the substance/substance group *Ethyl hydrogen fumarate calcium*.

| Supplier | Substance                       | Batch      | Sample ID          | Spectra |
|----------|---------------------------------|------------|--------------------|---------|
| Fagron   | Ethyl hydrogen fumarate calc... | 13B25-N08  | 21532 <sup>†</sup> | 20      |
| Euro OTC | Ethyl hydrogen fumarate calc... | 1310029-01 | 21562 <sup>†</sup> | 20      |
| Euro OTC | Ethyl hydrogen fumarate calc... | 1306012-01 | 21641 <sup>†</sup> | 20      |
| Euro OTC | Ethyl hydrogen fumarate calc... | 1510005    | 21938 <sup>†</sup> | 20      |
| Euro OTC | Ethyl hydrogen fumarate calc... | 1601011    | 22294 <sup>†</sup> | 20      |
| Euro OTC | Ethyl hydrogen fumarate calc... | 1510005-01 | not required       | 12      |

- 146 617 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Ethyl hydrogen fumarate calcium*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ethyl hydrogen fumarate calcium* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ethyl hydrogen fumarate calcium* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 112           | 0              | 146 617       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Ethyl hydrogen fumarate calcium* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.6429 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21532     | 21532               | 0.00                         | 42.01                           |
| 21562     | 21641               | 13.69                        | 41.56                           |
| 21641     | 21641               | 0.00                         | 39.20                           |
| 21938     | 21938               | 0.00                         | 46.39                           |
| 22294     | 22294               | 0.00                         | 46.94                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ethyl hydrogen fumarate magnesium**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21533-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ethyl hydrogen fumarate magnesium; Magnesii ethylhydrogenofumaras

### Special notes

When selecting the *Ethyl hydrogen fumarate magnesium* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ethyl hydrogen fumarate magnesium*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------|-----------|---------|--------------------|
| Fagron   | Ethyl hydrogen f... | 13G10-N01  | 21533     | 40      | 1411091            |
| Euro OTC | Ethyl hydrogen f... | 1510006    | 21937     | 40      | 20151030*          |
| Euro OTC | Ethyl hydrogen f... | 1510006-01 | 23008     | 40      | AR-18-FG-000547-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Ethyl hydrogen fumarate magnesium*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 166 spectra of 5 reference samples from the substance/substance group *Ethyl hydrogen fumarate magnesium*.

| Supplier | Substance                       | Batch            | Sample ID          | Spectra |
|----------|---------------------------------|------------------|--------------------|---------|
| Fagron   | Ethyl hydrogen fumarate magn... | 13G10-N01        | 21533 <sup>†</sup> | 20      |
| Euro OTC | Ethyl hydrogen fumarate magn... | 1306014-01       | 21642              | 60      |
| Euro OTC | Ethyl hydrogen fumarate magn... | 1510006          | 21937 <sup>†</sup> | 20      |
| Euro OTC | Ethyl hydrogen fumarate magn... | 1601010          | 22290              | 60      |
| Fagron   | Ethyl hydrogen fumarate magn... | 14H27-B04-299502 | not required       | 6       |

- 146 563 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Ethyl hydrogen fumarate magnesium*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ethyl hydrogen fumarate magnesium* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ethyl hydrogen fumarate magnesium* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 75            | 91             | 146 563       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Ethyl hydrogen fumarate magnesium* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 45.1807 % (> 43.3735 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21533     | 21533               | 0.00                         | 38.53                           |
| 21937     | 21937               | 0.00                         | 33.44                           |
| 23008     | 23008               | 0.00                         | 40.43                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das

alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Fampridine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20902-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Fampridine; Fampridinum

### Special notes

When selecting the *Fampridine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Fampridine*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate        |
|----------|------------|------------------|-----------|---------|--------------------|
| Fagron   | Fampridine | 13G26-N06        | 20902     | 40      | 1402686            |
| Fagron   | Fampridine | 14D11-B06-293750 | 21541     | 40      | 20140113           |
| Fagron   | Fampridine | 16D11-B07-318220 | 22491     | 40      | AR-16-FG-011566-01 |
| Fagron   | Fampridine | 16E25-B03-324097 | 22894     | 40      | 20160609           |
| Caelo    | Fampridine | 16276001         | 22905     | 40      | 20161024           |
| Caelo    | Fampridine | 16276001         | 23237     | 40      | 20161024           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Fampridine*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Fampridine*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Fagron   | Fampridine | 14D11-B06-293750 | 21541 <sup>†</sup> | 20      |
| Caelo    | Fampridine | 16276001         | 22881              | 40      |
| Fagron   | Fampridine | 16E25-B03-324097 | 22945              | 40      |
| Caelo    | Fampridine | 16276001         | 23074              | 40      |
| Caelo    | Fampridine | 172170           | 23653              | 40      |

- 146 549 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 7 spectra from 5 *Apo-Ident* customers from 7 batches from the substance/substance group *Fampridine*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance  | Batch            | Spectra |
|----------|------------|------------------|---------|
| Fagron   | Fampridine | 14D11-B06-296110 | 1       |
| Inresa   | Fampridine | 220825           | 1       |
| Fagron   | Fampridine | 14D11-B40-301641 | 1       |
| Caelo    | Fampridine | 15350001         | 1       |
| Caelo    | Fampridine | 15350002         | 1       |
| Fagron   | Fampridine | 16D11-B07        | 1       |
| Fagron   | Fampridine | 13C07-B02-289395 | 1       |

- 69 626 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Fampridine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Fampridine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 158           | 22             | 146 549       |
| <b>Type C</b> | 0              | 7             | 0              | 69 626        |

The substance/substance group *Fampridine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 87.7778 % (> 86.1111 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20902     | 20902               | 0.00                         | 73.22                           |
| 21541     | 20902               | 5.56                         | 73.60                           |
| 22491     | 22491               | 0.00                         | 70.03                           |
| 22894     | 22491               | 8.07                         | 72.34                           |
| 22905     | 22491               | 14.81                        | 72.56                           |
| 23237     | 22491               | 17.45                        | 71.79                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Finasteride (form III)**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20955-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Finasteride (form III); Finasteridum (Form III)

### Special notes

When selecting the *Finasteride (form III)* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Finasteride (form III)*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Finasteride (for... | 13I03-N01        | 20955     | 40      | 1411272     |
| Euro OTC | Finasteride (for... | 1403016-01       | 21626     | 40      | 1506004     |
| Fagron   | Finasteride (for... | 14A16-B40-295980 | 21742     | 40      | 20140317    |
| Euro OTC | Finasteride (for... | 1403016-02       | 21750     | 40      | 20140505    |
| Euro OTC | Finasteride (for... | 1605020          | 22565     | 40      | 20160613*   |

*continued on the next page*

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Finasteride (for... | 1610012          | 22856     | 40      | 20161116*   |
| Fagron   | Finasteride (for... | 14A16-B40-295980 | 21742SI   | 30      | 20140317    |
| Euro OTC | Finasteride (for... | 1403016-02       | 21750SI   | 36      | 20140505    |
| Euro OTC | Finasteride (for... | 1605020          | 22565SI   | 40      | 20160613*   |
| Euro OTC | Finasteride (for... | 1610012          | 22856SI   | 33      | 20161116*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 379 spectra of 10 reference samples from the substance/substance group *Finasteride (form III)*. These samples are listed above in the [calibration samples](#) section.
- 71 007 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 330 spectra of 11 reference samples from the substance/substance group *Finasteride (form III)*.

| Supplier | Substance              | Batch            | Sample ID            | Spectra |
|----------|------------------------|------------------|----------------------|---------|
| Fagron   | Finasteride (form III) | 12A04-N09        | 20589                | 40      |
| Euro OTC | Finasteride (form III) | 1403016-01       | 21626 <sup>†</sup>   | 20      |
| Fagron   | Finasteride (form III) | 14A16-B40-295980 | 21742 <sup>†</sup>   | 20      |
| Euro OTC | Finasteride (form III) | 1403016-02       | 21750 <sup>†</sup>   | 20      |
| Fagron   | Finasteride (form III) | 15J15-B02-320084 | 22594                | 40      |
| Fagron   | Finasteride (form III) | 15J15-B02-320084 | 22595                | 40      |
| Euro OTC | Finasteride (form III) | 1704004          | 23151                | 40      |
| Fagron   | Finasteride (form III) | 14A16-B40-295980 | 21742SI <sup>†</sup> | 15      |
| Euro OTC | Finasteride (form III) | 1403016-02       | 21750SI <sup>†</sup> | 15      |
| Fagron   | Finasteride (form III) | 15J15-B02-320084 | 22594SI              | 40      |
| Fagron   | Finasteride (form III) | 15J15-B02-320084 | 22595SI              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 399 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 8 spectra from 3 *Apo-Ident* customers from 7 batches from the substance/substance group *Finasteride (form III)*.

| Supplier                   | Substance              | Batch            | Spectra |
|----------------------------|------------------------|------------------|---------|
| Fagron                     | Finasteride (form III) | 14111305         | 1       |
| Fagron                     | Finasteride (form III) | 17011303         | 1       |
| FRagron                    | Finasteride (form III) | 13I03-N01        | 2       |
| Euro OTC                   | Finasteride (form III) | 1403016-02       | 1       |
| Euro OTC                   | Finasteride (form III) | 1411008-01       | 1       |
| Fagron                     | Finasteride (form III) | 14L23-B02-306981 | 1       |
| Shandong Northwest Manu... | Finasteride (form III) | FNA160604        | 1       |

- 69 625 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Finasteride (form III)* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Finasteride (form III)* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 379           | 0              | 71 007        |
| <b>Type B</b> | 0              | 330           | 0              | 146 399       |
| <b>Type C</b> | 0              | 7             | 1              | 69 625        |

The substance/substance group *Finasteride (form III)* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.4169 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.1818 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several

new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20955     | 20955               | 0.00                         | 39.48                           |
| 21626     | 21626               | 0.00                         | 52.18                           |
| 21742     | 21626               | 14.18                        | 49.46                           |
| 21750     | 21626               | 13.85                        | 49.09                           |
| 22565     | 22565               | 0.00                         | 50.69                           |
| 22856     | 22856               | 0.00                         | 52.19                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Fluconazole**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22360-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Fluconazole; Fluconazolum

### Special notes

When selecting the *Fluconazole* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Fluconazole*:

| Supplier | Substance   | Batch        | Sample ID | Spectra | Certificate        |
|----------|-------------|--------------|-----------|---------|--------------------|
| Audor    | Fluconazole | AP061502911F | 22360     | 40      | AR-16-FG-008733-01 |
| Audor    | Fluconazole | AP061502911F | 22596     | 40      | AR-16-FG-014225-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Fluconazole*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1551 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 5 reference samples from the substance/substance group *Fluconazole*.

| Supplier     | Substance   | Batch        | Sample ID          | Spectra |
|--------------|-------------|--------------|--------------------|---------|
| Audor Pharma | Fluconazole | AP061502911F | 22360 <sup>†</sup> | 20      |
| Audor Pharma | Fluconazole | AP061502911F | 22738              | 40      |
| Audor Pharma | Fluconazole | AP061502911F | 22360SI            | 60      |
| Audor Pharma | Fluconazole | AP061502911F | 22596SI            | 40      |
| Audor Pharma | Fluconazole | AP061502911F | 22738SI            | 40      |

- 146 529 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Fluconazole*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are docu-

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

mented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Fluconazole* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Fluconazole* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 175           | 25             | 146 529       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Fluconazole* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 87.5000 % (> 86.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22360     | 22360               | 0.00                         | 26.48                           |
| 22596     | 22596               | 0.00                         | 24.39                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Fluocinolonacetonid, micronized</b>                          |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 21031-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Fluocinolonacetonid, micronized; Fluocinoloni acetonidum micron.; Fluocinolonom acetonatum micron.

### Special notes

When selecting the *Fluocinolonacetonid, micronized* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Fluocinolonacetonid, micronized*:

| Supplier | Substance           | Batch       | Sample ID | Spectra | Certificate |
|----------|---------------------|-------------|-----------|---------|-------------|
| Euro OTC | Fluocinolonaceto... | 2804013E-01 | 21031     | 40      | 1404008     |
| Euro OTC | Fluocinolonaceto... | 2804013E-01 | 21077     | 40      | 20121206    |
| Caelo    | Fluocinolonaceto... | 12035003    | 21756     | 40      | 20120321    |
| Euro OTC | Fluocinolonaceto... | 2804013E-01 | 21822     | 40      | 20121206    |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Fluocinolonaacet... | 14L19-B04-307101 | 22267     | 30      | 20150219    |
| Caelo    | Fluocinolonaacet... | 162281           | 22637     | 40      | 20160907*   |
| Caelo    | Fluocinolonaacet... | 12035003         | 21756SI   | 33      | 20120321    |
| Euro OTC | Fluocinolonaacet... | 2804013E-01      | 21822SI   | 40      | 20121206    |
| Fagron   | Fluocinolonaacet... | 14L19-B04-307101 | 22267SI   | 30      | 20150219    |
| Caelo    | Fluocinolonaacet... | 162281           | 22637SI   | 30      | 20160907*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 363 spectra of 10 reference samples from the substance/substance group *Fluocinolonaacetoniid, micronized*. These samples are listed above in the [calibration samples](#) section.
- 71 023 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 353 spectra of 13 reference samples from the substance/substance group *Fluocinolonaacetoniid, micronized*.

| Supplier | Substance                         | Batch            | Sample ID            | Spectra |
|----------|-----------------------------------|------------------|----------------------|---------|
| Euro OTC | Fluocinolonaacetoniid, microni... | 2804013V-03      | 20243                | 40      |
| Caelo    | Fluocinolonaacetoniid, microni... | 12035003         | 21756 <sup>†</sup>   | 20      |
| Euro OTC | Fluocinolonaacetoniid, microni... | 2804013E-01      | 21822 <sup>†</sup>   | 20      |
| Euro OTC | Fluocinolonaacetoniid, microni... | 2804013E-01      | 21823                | 60      |
| Fagron   | Fluocinolonaacetoniid, microni... | 14L19-B04-307101 | 22267 <sup>†</sup>   | 15      |
| Fagron   | Fluocinolonaacetoniid, microni... | 14L19-B04-307101 | 23080                | 40      |
| Caelo    | Fluocinolonaacetoniid, microni... | 172130           | 23674                | 30      |
| Caelo    | Fluocinolonaacetoniid, microni... | 12035003         | 21756SI <sup>†</sup> | 15      |
| Euro OTC | Fluocinolonaacetoniid, microni... | 2804013E-01      | 21822SI <sup>†</sup> | 20      |
| Euro OTC | Fluocinolonaacetoniid, microni... | 2804013E-01      | 21823SI              | 46      |
| Fagron   | Fluocinolonaacetoniid, microni... | 14L19-B04-307101 | 22267SI <sup>†</sup> | 15      |
| Fagron   | Fluocinolonaacetoniid, microni... | 14L19-B04-307101 | 23080SI              | 20      |
| Caelo    | Fluocinolonaacetoniid, microni... | 172130           | 23674SI              | 12      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

- 146 376 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 18 spectra from 7 *Apo-Ident* customers from 13 batches from the substance/substance group *Fluocinolone acetonide, micronized*.

| Supplier      | Substance                             | Batch            | Spectra |
|---------------|---------------------------------------|------------------|---------|
| Fargon/Noweda | Fluocinolone acetonide, micronized... | 13L13-B35        | 1       |
| Fargon        | Fluocinolone acetonide, micronized... | 13L30-B35-295489 | 1       |
| Euro OTC      | Fluocinolone acetonide, micronized... | 1408022-01       | 2       |
| Euro OTC      | Fluocinolone acetonide, micronized... | 1408022-02       | 1       |
| Fargon        | Fluocinolone acetonide, micronized... | 14L19-B04        | 3       |
| Fargon/Kehr   | Fluocinolone acetonide, micronized... | 14L-19-B04       | 1       |
| Fargon        | Fluocinolone acetonide, micronized... | 14L19-B04-317248 | 2       |
| Fargon        | Fluocinolone acetonide, micronized... | 14L19-B04-615699 | 1       |
| Euro OTC      | Fluocinolone acetonide, micronized... | 2804013E-01      | 1       |
| Euro OTC      | Fluocinolone acetonide, micronized... | 2840013E-02      | 1       |
| Fargon        | Fluocinolone acetonide, micronized... | 13E22-N10        | 1       |
| Caelo         | Fluocinolone acetonide, micronized... | 2804013V-03      | 1       |
| Caelo         | Fluocinolone acetonide, micronized... | 12035003         | 2       |

- 69 615 spectra from 414 *Apo-Ident* customers from a total of 23 788 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Fluocinolone acetonide, micronized* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Fluocinolone acetonide, micronized* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 363           | 0              | 71 023        |
| <b>Type B</b> | 0              | 328           | 25             | 146 376       |
| <b>Type C</b> | 0              | 13            | 5              | 69 615        |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

The substance/substance group *Fluocinolonacetonid, micronized* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.3471 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 92.9178 % (> 92.0680 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21031            | 21031                      | 0.00                                | 35.63                                  |
| 21077            | 21031                      | 2.10                                | 35.75                                  |
| 21756            | 21031                      | 19.40                               | 40.61                                  |
| 21822            | 21031                      | 17.20                               | 40.23                                  |
| 22267            | 21031                      | 14.73                               | 42.33                                  |
| 22637            | 22637                      | 0.00                                | 48.01                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Folic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20370-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Folic acid; Acidum folicum

### Special notes

When selecting the *Folic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Folic acid*:

| Supplier | Substance  | Batch      | Sample ID | Spectra | Certificate |
|----------|------------|------------|-----------|---------|-------------|
| Fagron   | Folic acid | 12G17-N05  | 20767     | 40      | 20120727    |
| Euro OTC | Folic acid | 1401005-01 | 21288     | 40      | 20140131    |
| Euro OTC | Folic acid | 1508024    | 21891     | 40      | 20150902*   |
| Euro OTC | Folic acid | 1604036    | 22554     | 40      | 20160429*   |
| Euro OTC | Folic acid | 1611009    | 22868     | 40      | 20161201*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Folic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Folic acid*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Fagron   | Folic acid | 10F03-N13        | 20370              | 40      |
| Euro OTC | Folic acid | 1508024          | 21891 <sup>†</sup> | 20      |
| Euro OTC | Folic acid | 1608030          | 22818              | 40      |
| Fagron   | Folic acid | 16C03-B06-322513 | 23081              | 40      |

- 146 589 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 13 spectra from 11 *Apo-Ident* customers from 9 batches from the substance/substance group *Folic acid*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance  | Batch      | Spectra |
|----------|------------|------------|---------|
| Fagron   | Folic acid | 13g16-n02  | 1       |
| Fagron   | Folic acid | 10F03-N13  | 1       |
| Fagron   | Folic acid | 13A11-N01  | 1       |
| Euro OTC | Folic acid | 1307041-01 | 1       |
| Fagron   | Folic acid | 13G16-N02  | 4       |
| Euro OTC | Folic acid | 1401005-01 | 2       |
| Euro OTC | Folic acid | 1611009-01 | 1       |
| Fagron   | Folic acid | 16C03-B06  | 1       |
| Fagron   | Folic acid | UT11110182 | 1       |

- 69 620 spectra from 414 *Apo-Ident* customers from a total of 23 792 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Folic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Folic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 124           | 16             | 146 589       |
| <b>Type C</b> | 0              | 13            | 0              | 69 620        |

The substance/substance group *Folic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 88.5714 % (> 86.4286 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20767     | 21891               | 2.23                         | 66.25                           |
| 21288     | 21891               | 8.42                         | 63.08                           |
| 21891     | 21891               | 0.00                         | 64.13                           |
| 22554     | 22554               | 0.00                         | 56.10                           |
| 22868     | 22868               | 0.00                         | 65.45                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Fructose**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20074-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Fructose; Fructosum; Laevulosum

### Special notes

When selecting the *Fructose* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Fructose*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Euro OTC | Fructose  | 1212015-01 | 21281     | 40      | 20130111    |
| Euro OTC | Fructose  | 1509037    | 21934     | 40      | 20151027*   |
| Euro OTC | Fructose  | 1512009    | 22292     | 40      | 20160113*   |
| Caelo    | Fructose  | 160667     | 22481     | 40      | 20160425*   |
| Caelo    | Fructose  | 15084311   | 22490     | 40      | 20150316    |
| Euro OTC | Fructose  | 1701049    | 22986     | 40      | 20170213*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Fructose*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 426 spectra of 12 reference samples from the substance/substance group *Fructose*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Caelo    | Fructose  | 9302705          | 20074              | 45      |
| Euro OTC | Fructose  | 1509037          | 21934 <sup>†</sup> | 20      |
| Euro OTC | Fructose  | 1512009          | 22292 <sup>†</sup> | 20      |
| Caelo    | Fructose  | 160667           | 22481 <sup>†</sup> | 20      |
| Euro OTC | Fructose  | 1604024          | 22547              | 41      |
| Caelo    | Fructose  | 15271213         | 22583              | 40      |
| Euro OTC | Fructose  | 1607030          | 22693              | 40      |
| Fagron   | Fructose  | 16H05-B01-326259 | 23018              | 40      |
| Fagron   | Fructose  | 16H05-B01-326259 | 23082              | 40      |
| Euro OTC | Fructose  | 1705002          | 23391              | 40      |
| Caelo    | Fructose  | 171439           | 23422              | 40      |
| Caelo    | Fructose  | 171439           | 23673              | 40      |

- 146 303 spectra from a total of 3184 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 361 spectra from 92 *Apo-Ident* customers from 144 batches from the substance/substance group *Fructose*.

| Supplier            | Substance | Batch            | Spectra |
|---------------------|-----------|------------------|---------|
| Caelo               | Fructose  | 12132301         | 2       |
| Euro OTC            | Fructose  | 1509037-01       | 7       |
| Phoenix Goettin     | Fructose  | 14E01-B04-293505 | 2       |
| Caelo               | Fructose  | 14096205         | 4       |
| Caelo               | Fructose  | 15A16-B07-305241 | 1       |
| Jenne               | Fructose  | 1607030-01       | 2       |
| Fagron              | Fructose  | 7K21-N12         | 1       |
| Caelo               | Fructose  | 11258628         | 2       |
| Euro OTC            | Fructose  | 1201017-01       | 2       |
| phönix,29.10.12     | Fructose  | 1205022-01       | 1       |
| Caelo               | Fructose  | 12132313         | 5       |
| Caelo               | Fructose  | 12132317         | 2       |
| EuRho               | Fructose  | 1212015-01       | 1       |
| Euro OTC            | Fructose  | 1205022-01       | 1       |
| Caelo               | Fructose  | 12132325         | 3       |
| Fagron              | Fructose  | 12K28-N06        | 2       |
| Caelo               | Fructose  | 1309213394       | 1       |
| Caelo               | Fructose  | 1081501          | 1       |
| Synopharm           | Fructose  | 202A052          | 1       |
| Caelo               | Fructose  | 5061503          | 1       |
| Fagron              | Fructose  | 508Q-03394       | 1       |
| Fagron              | Fructose  | 516Q-03394       | 1       |
| Caelo               | Fructose  | 7051304          | 1       |
| Caelo               | Fructose  | 7111401          | 1       |
| Lihn/Reformhaus     | Fructose  | 713E-03394       | 2       |
| Caelo               | Fructose  | 9031504          | 1       |
| Caelo               | Fructose  | 10051401         | 1       |
| Caelo               | Fructose  | 10381011         | 1       |
| Caelo               | Fructose  | 10071201         | 1       |
| Caelo               | Fructose  | 10381013         | 1       |
| Anzag               | Fructose  | 10381013         | 1       |
| Gehe                | Fructose  | 11/07-N08        | 1       |
| Caelo               | Fructose  | 1114A03394       | 1       |
| Caelo               | Fructose  | 11071201         | 1       |
| Caelo               | Fructose  | 11258611         | 1       |
| Caelo               | Fructose  | 11258614         | 2       |
| Caelo               | Fructose  | 11258627         | 3       |
| Fagron              | Fructose  | 1170             | 1       |
| anzag am 12.06.2012 | Fructose  | 1201017-01       | 1       |
| Noweda              | Fructose  | 1205022-01       | 1       |
| Euro OTC            | Fructose  | 1209010-01       | 3       |
| Euro OTC            | Fructose  | 121201-01pzn     | 2       |
| Euro OTC            | Fructose  | 1212015-01       | 6       |
| euroct/gehe         | Fructose  | 1212015-01       | 1       |
| Anzag 05.03.13      | Fructose  | 12132301         | 1       |
| Ichthyol, Noweda    | Fructose  | 12132301         | 1       |
| Caelo               | Fructose  | 12132305         | 6       |
| Caelo               | Fructose  | 12132309         | 2       |
| Caelo               | Fructose  | 12132310         | 1       |
| Caelo               | Fructose  | 12132314         | 5       |
| Caelo               | Fructose  | 12132320         | 1       |
| Caelo               | Fructose  | 12132322         | 3       |

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| Supplier                   | Substance | Batch            | Spectra |
|----------------------------|-----------|------------------|---------|
| Caelo                      | Fructose  | 121e29-n08       | 1       |
| Fagron                     | Fructose  | 12A26-N04        | 1       |
| Gehe                       | Fructose  | 12B02-N07        | 1       |
| Gehe                       | Fructose  | 12E29-N08        | 4       |
| VDL                        | Fructose  | 12A26-N04        | 1       |
| Fagron                     | Fructose  | 12E29-N08        | 5       |
| Fagron                     | Fructose  | 12H01-N03        | 3       |
| Phönix                     | Fructose  | 12K28-N06        | 1       |
| Gehe                       | Fructose  | 12K28-N06        | 1       |
| Caelo                      | Fructose  | 13021304         | 1       |
| Euro OTC                   | Fructose  | 1307022-01       | 6       |
| Caelo                      | Fructose  | 13098902         | 3       |
| Caelo                      | Fructose  | 13098901         | 1       |
| Phoenix 22.12.14           | Fructose  | 1307022-01       | 1       |
| Fagron                     | Fructose  | 13098906         | 1       |
| Caelo                      | Fructose  | 13098904         | 1       |
| Caelo                      | Fructose  | 13098906         | 4       |
| Caelo                      | Fructose  | 13098909         | 1       |
| Caelo                      | Fructose  | 13098911         | 1       |
| Caelo                      | Fructose  | 13098913         | 4       |
| GEHE 17.06.2014            | Fructose  | 13098913         | 1       |
| Caelo                      | Fructose  | 13098914         | 3       |
| Caelo                      | Fructose  | 13098915         | 1       |
| Caelo                      | Fructose  | 13098917         | 3       |
| Caelo                      | Fructose  | 13098918         | 1       |
| Caelo                      | Fructose  | 13098922         | 1       |
| Caelo                      | Fructose  | 13098922         | 1       |
| Fagron                     | Fructose  | 1312A-03394      | 1       |
| Phönix                     | Fructose  | 13A28-N01        | 2       |
| Fagron                     | Fructose  | 13A28-N01        | 11      |
| 13.08.13                   | Fructose  | 13A28-N01        | 1       |
| fargon                     | Fructose  | 13C25-N03        | 1       |
| Fagron                     | Fructose  | 13C25-N03        | 3       |
| Fagron                     | Fructose  | 13E27-n07        | 1       |
| Fagron                     | Fructose  | 13E27-N07        | 2       |
| Alliance Health 13.02.2... | Fructose  | 13C25-N03        | 1       |
| Caelo                      | Fructose  | 13E27-N07        | 1       |
| Fagron                     | Fructose  | 13J18-B06        | 4       |
| Fagron                     | Fructose  | 13J18-B06-286894 | 1       |
| Fagron                     | Fructose  | 13j18B06286896   | 1       |
| Gehe                       | Fructose  | 13J18-B06-286896 | 1       |
| Fagron                     | Fructose  | 13J18-B06-286899 | 1       |
| Caelo                      | Fructose  | 13J18-B06-286896 | 1       |
| Euro OTC                   | Fructose  | 1401004-01       | 10      |
| Euro OTC                   | Fructose  | 140100401        | 1       |
| Phoenix 22.12.14           | Fructose  | 1401004-01       | 1       |
| Caelo                      | Fructose  | 14096201         | 4       |
| Caelo                      | Fructose  | 14096203         | 1       |
| Caelo                      | Fructose  | 14096207         | 1       |
| Caelo                      | Fructose  | 14096208         | 2       |
| Caelo                      | Fructose  | 14096211         | 1       |
| Caelo                      | Fructose  | 14096219         | 4       |
| Caelo                      | Fructose  | 14096223         | 5       |
| Euro OTC                   | Fructose  | 1410009-01       | 5       |
| Euro OTC                   | Fructose  | 141000901        | 3       |
| Jenne                      | Fructose  | 14A16-B07        | 1       |
| Caelo                      | Fructose  | 14305203         | 2       |
| Caelo                      | Fructose  | 14305204         | 1       |
| Fagron                     | Fructose  | 14E01-B04        | 7       |
| Fagron                     | Fructose  | 14E01-B04-29350  | 1       |

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| <b>Supplier</b>         | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|-------------------------|------------------|------------------|----------------|
| Fagron                  | Fructose         | 14E01-B04-293505 | 6              |
| Gehe                    | Fructose         | 14E01-B04-293506 | 2              |
| Fagron                  | Fructose         | 14E01-B04-293506 | 2              |
| Fagron                  | Fructose         | 14E01B04293506   | 1              |
| Fagron                  | Fructose         | 14E01-B04-297098 | 1              |
| Fagron                  | Fructose         | 14E1-B04-293506  | 1              |
| Fagron                  | Fructose         | 14K17-B99        | 6              |
| Alliance health         | Fructose         | 14K17-B99-300913 | 4              |
| Fagron                  | Fructose         | 15/21-B01        | 1              |
| Caelo                   | Fructose         | 1503045-01       | 2              |
| Euro OTC                | Fructose         | 1503045-01       | 6              |
| Caelo                   | Fructose         | 15084301         | 1              |
| Caelo                   | Fructose         | 15084305         | 3              |
| Caelo                   | Fructose         | 15084312         | 1              |
| Caelo                   | Fructose         | 1509037-01       | 2              |
| Euro OTC                | Fructose         | 1512009-01       | 5              |
| Caelo                   | Fructose         | 152711201        | 1              |
| Caelo                   | Fructose         | 15271205         | 3              |
| Caelo                   | Fructose         | 15271208         | 1              |
| Caelo                   | Fructose         | 15271209         | 1              |
| Caelo                   | Fructose         | 15271213         | 6              |
| Caelo                   | Fructose         | 15271214         | 2              |
| Caelo                   | Fructose         | 15271215         | 1              |
| Caelo                   | Fructose         | 15A16-B07        | 1              |
| Gatt Koller             | Fructose         | 1544/05141914    | 1              |
| Fagron                  | Fructose         | 15A16-B07        | 2              |
| Jenne                   | Fructose         | 15A16-B07        | 1              |
| Fagron                  | Fructose         | 15A16-B07-305241 | 1              |
| Fagron                  | Fructose         | 15A16-B07-308950 | 1              |
| Fagron                  | Fructose         | 15I21-B01        | 2              |
| Fagron                  | Fructose         | 15I21-B01-312701 | 1              |
| Phoenix                 | Fructose         | 15I21-B01        | 1              |
| Fagron                  | Fructose         | 15I21-B01-323020 | 1              |
| Fagron                  | Fructose         | 15I21-B01-323021 | 3              |
| Fagron                  | Fructose         | 15I21-B01-323021 | 1              |
| Euro OTC                | Fructose         | 1604024-01       | 2              |
| Ebert & Jacobi 08.08.16 | Fructose         | 1604024-01       | 1              |
| Caelo                   | Fructose         | 16066103         | 2              |
| EuRho/Noweda            | Fructose         | 1604024-01       | 1              |
| Caelo                   | Fructose         | 16066106         | 5              |
| Caelo                   | Fructose         | 16066107         | 1              |
| Euro OTC                | Fructose         | 1607030-01       | 3              |
| Caelo                   | Fructose         | 1610033-01       | 2              |
| Euro OTC                | Fructose         | 1610033-01       | 2              |
| Caelo                   | Fructose         | 17007702         | 1              |
| Caelo                   | Fructose         | 18021501         | 1              |
| Caelo                   | Fructose         | 21051303         | 1              |
| Caelo                   | Fructose         | 20081402         | 1              |
| Fagron                  | Fructose         | 3014Q-03394      | 1              |
| Gatt-Koller / Phoenix   | Fructose         | 3156/0813        | 1              |
| Caelo                   | Fructose         | 31031401         | 1              |
| Caelo                   | Fructose         | 3313U-03394      | 1              |
| Phoenix 05.08.2014      | Fructose         | FR1336122        | 3              |
| fragon                  | Fructose         | FR1413072        | 1              |
| Fagron                  | Fructose         | FR1443072        | 1              |
| Caelo                   | Fructose         | Fructose2        | 1              |
| Caelo                   | Fructose         | Fructose1        | 1              |
| Fagron                  | Fructose         | FR1413072        | 1              |
| Gehe                    | Fructose         | K43298821        | 1              |
| Fagron                  | Fructose         | K43298821        | 2              |

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| Supplier   | Substance | Batch            | Spectra |
|------------|-----------|------------------|---------|
| Sanacorp   | Fructose  | K43537721        | 1       |
| Fagron     | Fructose  | K43537721        | 1       |
| Caelo      | Fructose  | 12H01-N03        | 1       |
| Caelo      | Fructose  | 13A28-N01        | 1       |
| Caelo      | Fructose  | 14305201         | 1       |
| Caelo      | Fructose  | 15084308         | 1       |
| Caelo      | Fructose  | 14305206         | 1       |
| Caelo      | Fructose  | 15084311         | 1       |
| Fagron     | Fructose  | 1107-N06         | 1       |
| Caelo      | Fructose  | 11I07-N06        | 1       |
| Caelo      | Fructose  | 13C25-N03        | 2       |
| Fagron     | Fructose  | 13J18-B06-286896 | 1       |
| Beiersdorf | Fructose  | 14096208         | 1       |

- 69 272 spectra from 414 *Apo-Ident* customers from a total of 23 657 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Fructose* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Fructose* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 426           | 0              | 146 303       |
| <b>Type C</b> | 0              | 360           | 1              | 69 272        |

The substance/substance group *Fructose* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.5915 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 99.7230 % (> 98.8920 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21281     | 22986               | 6.28                         | 35.34                           |
| 21934     | 21934               | 0.00                         | 30.62                           |
| 22292     | 22292               | 0.00                         | 40.40                           |
| 22481     | 22481               | 0.00                         | 37.01                           |
| 22490     | 22292               | 3.46                         | 38.90                           |
| 22986     | 22986               | 0.00                         | 37.33                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Furosemide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20944-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Furosemide; Furosemidum

### Special notes

When selecting the *Furosemide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Furosemide*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate |
|----------|------------|------------------|-----------|---------|-------------|
| Fagron   | Furosemide | 13A22-N08        | 20944     | 40      | 1401379     |
| Fagron   | Furosemide | 14K10-B02-301746 | 21819     | 40      | 20141215    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Furosemide*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Furosemide*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Fagron   | Furosemide | 11B18-N04        | 20241              | 40      |
| Fagron   | Furosemide | 14K10-B02-301746 | 21819 <sup>†</sup> | 20      |
| Fagron   | Furosemide | 16B15-B06-322860 | 23083              | 40      |
| Fagron   | Furosemide | 16B15-B06-322860 | 23084              | 40      |

- 146 589 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 15 spectra from 11 *Apo-Ident* customers from 11 batches from the substance/substance group *Furosemide*.

| Supplier | Substance  | Batch    | Spectra |
|----------|------------|----------|---------|
| Fagron   | Furosemide | 1095H2RI | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier                   | Substance  | Batch            | Spectra |
|----------------------------|------------|------------------|---------|
| IPCA/Noweda                | Furosemide | 11D29-N08        | 1       |
| Fagron                     | Furosemide | 11K21-N26        | 1       |
| Phönix                     | Furosemide | 12a18-n03        | 1       |
| Alliance Healthcare/Hed... | Furosemide | 12/13-N06        | 1       |
| Fagron                     | Furosemide | 12A18-N03        | 1       |
| Fagron                     | Furosemide | 12I13-No6        | 1       |
| Fagron                     | Furosemide | 13A22-N08        | 4       |
| Fagron                     | Furosemide | 13E28-B40        | 2       |
| Fagron                     | Furosemide | 13E28-B40-295538 | 1       |
| Fagron                     | Furosemide | 13E28-B40-289433 | 1       |

- 69 618 spectra from 414 *Apo-Ident* customers from a total of 23 791 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Furosemide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Furosemide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 140           | 0              | 146 589       |
| <b>Type C</b> | 0              | 15            | 0              | 69 618        |

The substance/substance group *Furosemide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.7143 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20944     | 20944               | 0.00                         | 67.96                           |
| 21819     | 20944               | 6.43                         | 66.23                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Fusidic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20780-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Fusidic acid; Acidum fusidicum; Acidum fusidinicum

### Special notes

When selecting the *Fusidic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Fusidic acid*:

| Supplier | Substance    | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------|------------------|-----------|---------|-------------|
| Fagron   | Fusidic acid | 12G04-N01        | 20780     | 40      | 1401162     |
| Fagron   | Fusidic acid | 13L13-B01-289513 | 21733     | 40      | 20140113    |
| Fagron   | Fusidic acid | 14E01-B08-299791 | 21897     | 40      | 20140605    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Fusidic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 3 reference samples from the substance/substance group *Fusidic acid*.

| Supplier | Substance    | Batch            | Sample ID          | Spectra |
|----------|--------------|------------------|--------------------|---------|
| Fagron   | Fusidic acid | 13L13-B01-289513 | 21733 <sup>†</sup> | 20      |
| Fagron   | Fusidic acid | 14E01-B08-299791 | 21897 <sup>†</sup> | 20      |
| Fagron   | Fusidic acid | 15I10-B02-322112 | 23069              | 40      |

- 146 649 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 12 spectra from 7 *Apo-Ident* customers from 10 batches from the substance/substance group *Fusidic acid*.

| Supplier | Substance    | Batch            | Spectra |
|----------|--------------|------------------|---------|
| Fagron   | Fusidic acid | 4113U-07034      | 1       |
| Fagron   | Fusidic acid | 13L13-B01-289513 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier       | Substance    | Batch            | Spectra |
|----------------|--------------|------------------|---------|
| Fagron         | Fusidic acid | 14E01-B08-299791 | 2       |
| Fagron         | Fusidic acid | 116E-03682       | 1       |
| Fagron         | Fusidic acid | 1510-B02319231   | 1       |
| Ebert 24.08.16 | Fusidic acid | 1510-B02319452   | 1       |
| Fagron         | Fusidic acid | 12B23-N03        | 1       |
| Fagron         | Fusidic acid | 12G04-No1        | 1       |
| Fagron         | Fusidic acid | 13A07-N10        | 2       |
| Fagron         | Fusidic acid | 13H19-N05        | 1       |

- 69 621 spectra from 414 *Apo-Ident* customers from a total of 23 791 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Fusidic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Fusidic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 12            | 0              | 69 621        |

The substance/substance group *Fusidic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20780     | 20780               | 0.00                         | 30.56                           |
| 21733     | 20780               | 4.81                         | 29.04                           |
| 21897     | 20780               | 14.80                        | 27.75                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Gelatine, white**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20206-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Gelatine, white; Gelatina alba

### Special notes

When selecting the *Gelatine, white* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Gelatine, white*:

| Supplier | Substance       | Batch    | Sample ID | Spectra | Certificate        |
|----------|-----------------|----------|-----------|---------|--------------------|
| Caelo    | Gelatine, white | 11334025 | 20898     | 40      | 20111214           |
| Caelo    | Gelatine, white | 15320504 | 22499     | 40      | AR-16-FG-014461-01 |
| Caelo    | Gelatine, white | 15320504 | 22582     | 40      | AR-16-FG-011564-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Gelatine, white*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 45 spectra of 2 reference samples from the substance/substance group *Gelatine, white*.

| Supplier | Substance       | Batch    | Sample ID          | Spectra |
|----------|-----------------|----------|--------------------|---------|
| Caelo    | Gelatine, white | 10051107 | 20206              | 40      |
| Caelo    | Gelatine, white | 15320504 | 22582 <sup>†</sup> | 5       |

- 146 684 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 23 spectra from 16 *Apo-Ident* customers from 16 batches from the substance/substance group *Gelatine, white*.

| Supplier   | Substance       | Batch      | Spectra |
|------------|-----------------|------------|---------|
| EuRho / 20 | Gelatine, white | 1106021-01 | 1       |
| Caelo      | Gelatine, white | 14130901   | 2       |
| Caelo      | Gelatine, white | 14130912   | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier          | Substance       | Batch       | Spectra |
|-------------------|-----------------|-------------|---------|
| Caelo             | Gelatine, white | 15084801    | 1       |
| Caelo             | Gelatine, white | 15084806    | 1       |
| Caelo             | Gelatine, white | 15320504    | 1       |
| Caelo             | Gelatine, white | 11019308    | 1       |
| Caelo             | Gelatine, white | 11019319    | 1       |
| Caelo             | Gelatine, white | 11019322    | 1       |
| Euro OTC          | Gelatine, white | 1106021-01  | 2       |
| Caelo             | Gelatine, white | 11314516    | 1       |
| Caelo             | Gelatine, white | 11334020    | 1       |
| Caelo             | Gelatine, white | 11334025    | 3       |
| Phönix 13.05.2013 | Gelatine, white | 12332564    | 1       |
| Caelo             | Gelatine, white | 12354401    | 1       |
| Caelo             | Gelatine, white | 12354507    | 3       |
| Caelo             | Gelatine, white | 4110I-01578 | 1       |

- 69 610 spectra from 414 *Apo-Ident* customers from a total of 23 787 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Gelatine, white* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Gelatine, white* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 11            | 34             | 146 684       |
| <b>Type C</b> | 0              | 16            | 7              | 69 610        |

The substance/substance group *Gelatine, white* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 24.4444 % (> 17.7778 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 69.5652 % (> 56.5217 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20898     | 22582               | 6.48                         | 19.23                           |
| 22499     | 22499               | 0.00                         | 17.04                           |
| 22582     | 22582               | 0.00                         | 17.45                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Gentamicin sulfate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20640-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Gentamicin sulfate; Gentamicin sulphate; Gentamicini sulfas; Gentamycinum sulfuricum

### Special notes

When selecting the *Gentamicin sulfate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Gentamicin sulfate*:

| Supplier | Substance          | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------------|------------------|-----------|---------|-------------|
| Fagron   | Gentamicin sulfate | 12B21-N02        | 20661     | 40      | 1411075     |
| Euro OTC | Gentamicin sulfate | 1305047-01       | 21081     | 40      | 20130919    |
| Caelo    | Gentamicin sulfate | 13205003         | 21580     | 40      | 20130723    |
| Euro OTC | Gentamicin sulfate | 1305047-03       | 21582     | 40      | 1411076     |
| Fagron   | Gentamicin sulfate | 14E08-B03-294848 | 21684     | 40      | 20140616    |

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| Supplier | Substance          | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------------|------------------|-----------|---------|-------------|
| Euro OTC | Gentamicin sulfate | 1506016          | 21837     | 40      | 0000010321  |
| Caelo    | Gentamicin sulfate | 14353504         | 22604     | 40      | 20150119    |
| Euro OTC | Gentamicin sulfate | 1610036          | 22857     | 40      | 20161124*   |
| Fagron   | Gentamicin sulfate | 16B29-B01-328731 | 23210     | 40      | 20160411    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 360 spectra of 9 reference samples from the substance/substance group *Gentamicin sulfate*. These samples are listed above in the [calibration samples](#) section.
- 71 026 spectra from a total of 1543 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 635 spectra of 16 reference samples from the substance/substance group *Gentamicin sulfate*.

| Supplier    | Substance          | Batch            | Sample ID          | Spectra |
|-------------|--------------------|------------------|--------------------|---------|
| Caelo       | Gentamicin sulfate | 73402189         | 20008              | 50      |
| Caelo       | Gentamicin sulfate | 9115106          | 20108              | 40      |
| Euro OTC    | Gentamicin sulfate | 2911034-01       | 20223              | 40      |
| Caelo       | Gentamicin sulfate | 11113309         | 20640              | 40      |
| zu erfassen | Gentamicin sulfate | pending          | 21016              | 20      |
| Fagron      | Gentamicin sulfate | 13I19-B05-286565 | 21578              | 60      |
| Caelo       | Gentamicin sulfate | 13205003         | 21580 <sup>†</sup> | 20      |
| Euro OTC    | Gentamicin sulfate | 1305047-03       | 21582 <sup>†</sup> | 20      |
| Fagron      | Gentamicin sulfate | 14E08-B03-294848 | 21684 <sup>†</sup> | 20      |
| Euro OTC    | Gentamicin sulfate | 1305047-03       | 21697              | 45      |
| Euro OTC    | Gentamicin sulfate | 1506016          | 21837 <sup>†</sup> | 20      |
| Euro OTC    | Gentamicin sulfate | 1604054          | 22568              | 40      |
| Caelo       | Gentamicin sulfate | 170996           | 23335              | 40      |
| Fagron      | Gentamicin sulfate | 13I19-B05-286565 | 21578SI            | 60      |
| Caelo       | Gentamicin sulfate | 13205003         | 21580SI            | 60      |
| Euro OTC    | Gentamicin sulfate | 1506016          | 21837SI            | 60      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

- 146 094 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 574 spectra from 245 *Apo-Ident* customers from 164 batches from the substance/substance group *Gentamicin sulfate*.

| Supplier                   | Substance          | Batch            | Spectra |
|----------------------------|--------------------|------------------|---------|
| Euro OTC                   | Gentamicin sulfate | 4988304          | 1       |
| Caelo                      | Gentamicin sulfate | 7011505          | 1       |
| Euro OTC                   | Gentamicin sulfate | 1205021-02       | 18      |
| Caelo                      | Gentamicin sulfate | 12146602         | 9       |
| Caelo                      | Gentamicin sulfate | 12146604         | 6       |
| Fagron                     | Gentamicin sulfate | 12D26-N05        | 11      |
| Fargron/AHD                | Gentamicin sulfate | 12G04-N16        | 1       |
| Fujian Fukang Pharmaceu... | Gentamicin sulfate | 12G04-N16        | 2       |
| Fagron                     | Gentamicin sulfate | 13/19-B05        | 1       |
| Fagron                     | Gentamicin sulfate | 13/19-B05-286568 | 1       |
| Bombastus                  | Gentamicin sulfate | 13024-N05        | 1       |
| Noweda                     | Gentamicin sulfate | 1305005          | 1       |
| PHOENIX 10.03.2014         | Gentamicin sulfate | 1305047          | 1       |
| Gehe am 24.2.14            | Gentamicin sulfate | 1305047-01       | 1       |
| Euro OTC                   | Gentamicin sulfate | 1305047-01       | 11      |
| Euro OTC                   | Gentamicin sulfate | 1305047-03       | 12      |
| Euro OTC                   | Gentamicin sulfate | 130504703        | 2       |
| Euroo/Phoenix              | Gentamicin sulfate | 1305047-03       | 1       |
| Phoenix                    | Gentamicin sulfate | 1305047-03       | 1       |
| Anzag                      | Gentamicin sulfate | 1305047-03       | 1       |
| Caelo                      | Gentamicin sulfate | 1305047-03       | 2       |
| Sanacorp 06.01.15 EK 6,20  | Gentamicin sulfate | 1305047-03       | 1       |
| Sanacorp                   | Gentamicin sulfate | 1305047-03       | 1       |
| Caelo                      | Gentamicin sulfate | 13189606         | 7       |
| Herbasinica                | Gentamicin sulfate | 13189608         | 1       |
| Sanacorp                   | Gentamicin sulfate | 13189608         | 1       |
| Caelo                      | Gentamicin sulfate | 13189608         | 4       |
| Phönix                     | Gentamicin sulfate | 13189611         | 1       |
| Phönix Gotha               | Gentamicin sulfate | 13189611         | 1       |
| Caelo                      | Gentamicin sulfate | 13189611         | 10      |
| Noweda                     | Gentamicin sulfate | 13189611         | 1       |
| Caelo                      | Gentamicin sulfate | 13189612         | 14      |
| Noweda                     | Gentamicin sulfate | 13189612         | 1       |
| Caelo                      | Gentamicin sulfate | 13189614         | 2       |
| Caelo                      | Gentamicin sulfate | 13189613         | 1       |
| Fagron                     | Gentamicin sulfate | 1319-B05-286565  | 1       |
| Caelo                      | Gentamicin sulfate | 13205003         | 8       |
| Caelo                      | Gentamicin sulfate | 13205004         | 1       |
| Caelo                      | Gentamicin sulfate | 13205005         | 12      |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier                   | Substance          | Batch            | Spectra |
|----------------------------|--------------------|------------------|---------|
| AHD 29.10.14 EK6,12        | Gentamicin sulfate | 13205004         | 1       |
| AHD                        | Gentamicin sulfate | 13205005         | 2       |
| Caelo                      | Gentamicin sulfate | 13205006         | 5       |
| Caelo                      | Gentamicin sulfate | 13205007         | 2       |
| Fagron                     | Gentamicin sulfate | 13f13-N01        | 1       |
| Fagron                     | Gentamicin sulfate | 13D24-N05        | 10      |
| Fagron                     | Gentamicin sulfate | 13I19-B05        | 1       |
| Caelo                      | Gentamicin sulfate | 13I19-B05-286565 | 1       |
| Euro OTC                   | Gentamicin sulfate | 1407024          | 1       |
| Euro OTC                   | Gentamicin sulfate | 1407024-01       | 2       |
| Euro                       | Gentamicin sulfate | 1407024-01       | 1       |
| Euro OTC                   | Gentamicin sulfate | 1407024-03       | 2       |
| Euro OTC                   | Gentamicin sulfate | 140702403        | 1       |
| Euro OTC                   | Gentamicin sulfate | 140702404        | 2       |
| Noweda                     | Gentamicin sulfate | 140702404        | 1       |
| Euro OTC                   | Gentamicin sulfate | 1407024-04       | 6       |
| Euro OTC                   | Gentamicin sulfate | 1407024-4        | 1       |
| Fagron                     | Gentamicin sulfate | 14081307         | 1       |
| Caelo                      | Gentamicin sulfate | 14081307         | 1       |
| Caelo                      | Gentamicin sulfate | 14353502         | 2       |
| Caelo                      | Gentamicin sulfate | 14353503         | 12      |
| Caelo                      | Gentamicin sulfate | 143533504        | 1       |
| Caelo                      | Gentamicin sulfate | 14353504         | 7       |
| Noweda                     | Gentamicin sulfate | 14353504         | 1       |
| Fagron                     | Gentamicin sulfate | 14A30-B04        | 2       |
| Caelo                      | Gentamicin sulfate | 14353505         | 2       |
| Fagron                     | Gentamicin sulfate | 14A30-B04-290861 | 3       |
| Fujian Fukang Pharmacea... | Gentamicin sulfate | 14A30-B04-290861 | 1       |
| Fagron                     | Gentamicin sulfate | 14E08-B03        | 2       |
| Fagron                     | Gentamicin sulfate | 14E08-B03-294835 | 2       |
| Caelo                      | Gentamicin sulfate | 14E08-B03-294841 | 1       |
| Fagron                     | Gentamicin sulfate | 14E08-B03-294841 | 2       |
| Fagron                     | Gentamicin sulfate | 14E08-B03-294848 | 3       |
| Fagron                     | Gentamicin sulfate | 14E08-B03-300619 | 1       |
| Fagron                     | Gentamicin sulfate | 14e08b03300619   | 1       |
| Fujian Fukang Pharmacea... | Gentamicin sulfate | 14E08-B03-300619 | 1       |
| Fagron                     | Gentamicin sulfate | 14K28-B06        | 3       |
| Yantai Justaware Pharma... | Gentamicin sulfate | 14K28-B06        | 1       |
| Fagron                     | Gentamicin sulfate | 14K28-B06-301951 | 1       |
| Caelo                      | Gentamicin sulfate | 14K28-B06-303636 | 1       |
| Fagron                     | Gentamicin sulfate | 14K28-B06-303640 | 1       |
| Fagron                     | Gentamicin sulfate | 14k28-b06-303640 | 1       |
| Euro OTC                   | Gentamicin sulfate | 14K28-B06-303640 | 2       |
| Caelo                      | Gentamicin sulfate | 14K28-B06-303646 | 3       |
| Fagron                     | Gentamicin sulfate | 14K28-B06-303646 | 3       |
| Fagron                     | Gentamicin sulfate | 14K28B06303646   | 2       |
| Euro OTC                   | Gentamicin sulfate | 150601601        | 1       |
| Euro OTC                   | Gentamicin sulfate | 1506016-01       | 7       |
| Caelo                      | Gentamicin sulfate | 1506016-01       | 2       |
| Euro OTC                   | Gentamicin sulfate | 1506016-02       | 22      |
| Euro OTC                   | Gentamicin sulfate | 150601602        | 1       |
| Caelo                      | Gentamicin sulfate | 15226501         | 9       |
| Phoenix                    | Gentamicin sulfate | 15226501         | 1       |
| Caelo                      | Gentamicin sulfate | 15226502         | 11      |
| Phoenix                    | Gentamicin sulfate | 15226502         | 1       |
| Caelo                      | Gentamicin sulfate | 15226508         | 2       |
| PHÖNIX                     | Gentamicin sulfate | 15226514         | 1       |
| Caelo                      | Gentamicin sulfate | 15226514         | 2       |
| Gehe                       | Gentamicin sulfate | 15226517         | 1       |
| Caelo                      | Gentamicin sulfate | 15226518         | 1       |

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| Supplier                   | Substance          | Batch            | Spectra |
|----------------------------|--------------------|------------------|---------|
| Caelo                      | Gentamicin sulfate | 15258802         | 11      |
| Fagron                     | Gentamicin sulfate | 15258802         | 1       |
| Caesar&Loretz GmbH,25.0... | Gentamicin sulfate | 15258802         | 1       |
| Caelo                      | Gentamicin sulfate | 15258803         | 8       |
| Caelo                      | Gentamicin sulfate | 15258808         | 2       |
| Caelo                      | Gentamicin sulfate | 15258809         | 1       |
| Sanacorp                   | Gentamicin sulfate | 15258808         | 1       |
| Caelo                      | Gentamicin sulfate | 15258810         | 4       |
| Caelo                      | Gentamicin sulfate | 15258813         | 3       |
| Caelo                      | Gentamicin sulfate | 15258815         | 2       |
| Caelo                      | Gentamicin sulfate | 15258816         | 2       |
| Phoenix                    | Gentamicin sulfate | 15258816         | 1       |
| Fagron                     | Gentamicin sulfate | 15B03-B07        | 1       |
| Fagron                     | Gentamicin sulfate | 15b03-b07-309482 | 1       |
| Fagron                     | Gentamicin sulfate | 15B03-B07-309482 | 1       |
| Caelo                      | Gentamicin sulfate | 15B03-B07-309482 | 1       |
| Fagron                     | Gentamicin sulfate | 15E04-B05-316255 | 2       |
| Fagron                     | Gentamicin sulfate | 15G29-B09-320305 | 3       |
| Fagron                     | Gentamicin sulfate | 15G29-B09-322928 | 1       |
| Fagron                     | Gentamicin sulfate | 15G29-B09-326632 | 1       |
| Euro OTC                   | Gentamicin sulfate | 16004054-01      | 1       |
| Euro OTC                   | Gentamicin sulfate | 16004054-02      | 1       |
| Euro OTC                   | Gentamicin sulfate | 1604054-01       | 8       |
| Caelo                      | Gentamicin sulfate | 1604054-01       | 2       |
| Eurimpharm1                | Gentamicin sulfate | 1604054-01       | 1       |
| Euro OTC                   | Gentamicin sulfate | 1604054-02       | 2       |
| Caelo                      | Gentamicin sulfate | 1610036-01       | 1       |
| Euro OTC                   | Gentamicin sulfate | 1610036-01       | 3       |
| Fagron                     | Gentamicin sulfate | 16B29-B01-328731 | 1       |
| Caelo                      | Gentamicin sulfate | 17081502         | 1       |
| Caelo                      | Gentamicin sulfate | 20161102-4       | 1       |
| Caelo                      | Gentamicin sulfate | 23012015E        | 1       |
| Sanacorp                   | Gentamicin sulfate | 28/AKD11         | 1       |
| Fagron                     | Gentamicin sulfate | FG1212646        | 1       |
| Caelo                      | Gentamicin sulfate |                  | 2       |
| Caelo                      | Gentamicin sulfate | 31032014E        | 1       |
| Caelo                      | Gentamicin sulfate | 4563125          | 1       |
| Fagron                     | Gentamicin sulfate | FG1305122        | 1       |
| Fagron                     | Gentamicin sulfate | 11K21-N17        | 2       |
| Euro OTC                   | Gentamicin sulfate | 1205021-01       | 11      |
| Caelo                      | Gentamicin sulfate | 1205021-01       | 1       |
| Caelo                      | Gentamicin sulfate | 1216602          | 1       |
| Caelo                      | Gentamicin sulfate | 12G04-N16        | 2       |
| Euro OTC                   | Gentamicin sulfate | FG11112482       | 1       |
| Sanacorp                   | Gentamicin sulfate | 13189606         | 1       |
| Caelo                      | Gentamicin sulfate | 13189607         | 11      |
| Fagron                     | Gentamicin sulfate | 13I19-B05-286568 | 1       |
| Fagron                     | Gentamicin sulfate | 14A30-B04-290858 | 1       |
| Fagron                     | Gentamicin sulfate | 11604054-01      | 1       |
| EuRho                      | Gentamicin sulfate | 1305047-01       | 1       |
| Caelo                      | Gentamicin sulfate | 1435303          | 1       |
| Caesar & Loretz GmbH       | Gentamicin sulfate | 14353503         | 1       |
| Fagron                     | Gentamicin sulfate | 14a30-b04-290858 | 1       |
| Fagron                     | Gentamicin sulfate | 14k28-B06-303640 | 1       |
| Caesar&Loretz GmbH         | Gentamicin sulfate | 15226501         | 1       |
| Fagron                     | Gentamicin sulfate | 15803-B07-309482 | 1       |
| Caelo                      | Gentamicin sulfate | 6082013C         | 1       |
| Caelo                      | Gentamicin sulfate | 3714I-01582      | 1       |
| Euro OTC                   | Gentamicin sulfate | 80616-2          | 1       |
| Caelo                      | Gentamicin sulfate | 100017814        | 1       |

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| <b>Supplier</b>     | <b>Substance</b>   | <b>Batch</b> | <b>Spectra</b> |
|---------------------|--------------------|--------------|----------------|
| Caelo               | Gentamicin sulfate | 9115112      | 1              |
| Phönix Gotha        | Gentamicin sulfate | 10017817     | 1              |
| Caelo               | Gentamicin sulfate | 10017820     | 1              |
| Fagron              | Gentamicin sulfate | 10A29-N06    | 1              |
| Euro OTC            | Gentamicin sulfate | 1007036-03   | 1              |
| Fagron              | Gentamicin sulfate | 11/09N10     | 1              |
| Fagron              | Gentamicin sulfate | 11/09-N10    | 1              |
| Noweda              | Gentamicin sulfate | 1106016-01   | 1              |
| Euro OTC            | Gentamicin sulfate | 1106016-01   | 6              |
| Caelo               | Gentamicin sulfate | 1106016-01   | 1              |
| Fagron              | Gentamicin sulfate | 1106016-01   | 1              |
| Euro OTC            | Gentamicin sulfate | 1106016-02   | 3              |
| Euro OTC            | Gentamicin sulfate | 1106016-03   | 3              |
| Caelo               | Gentamicin sulfate | 1106016-03   | 1              |
| Caelo               | Gentamicin sulfate | 11113303     | 2              |
| Euro OTC            | Gentamicin sulfate | 110616-01    | 1              |
| Caelo               | Gentamicin sulfate | 111113309    | 1              |
| Caelo               | Gentamicin sulfate | 11113304     | 4              |
| Caelo               | Gentamicin sulfate | 11113308     | 5              |
| Phönix              | Gentamicin sulfate | 11113309     | 1              |
| phönix, 19.11.2012  | Gentamicin sulfate | 1160616-03   | 1              |
| Fagron              | Gentamicin sulfate | 11k21-n17    | 3              |
| Großhandel          | Gentamicin sulfate | 11K21-N17    | 1              |
| Sanacorp            | Gentamicin sulfate | 1205021      | 1              |
| Gehe                | Gentamicin sulfate | 1205021-01   | 1              |
| Bombastus           | Gentamicin sulfate | 1205021-01   | 1              |
| Gehe                | Gentamicin sulfate | 1205021-02   | 1              |
| Caelo               | Gentamicin sulfate | 1205021-02   | 3              |
| Fagron              | Gentamicin sulfate | 1205021-02   | 3              |
| Euro OTC            | Gentamicin sulfate |              | 1              |
| phönix              | Gentamicin sulfate | 1214605      | 1              |
| Anzag               | Gentamicin sulfate | 12146602     | 1              |
| Noweda              | Gentamicin sulfate | 12146602     | 1              |
| Phönix              | Gentamicin sulfate | 12146602     | 1              |
| vdl                 | Gentamicin sulfate | 12146602     | 1              |
| Gehe                | Gentamicin sulfate | 12146604     | 1              |
| Caelo               | Gentamicin sulfate | 12146605     | 6              |
| Gehe                | Gentamicin sulfate | 12146605     | 1              |
| Phönix Gotha        | Gentamicin sulfate | 12146611     | 1              |
| Caelo               | Gentamicin sulfate | 12146611     | 12             |
| Caelo               | Gentamicin sulfate | 12146612     | 4              |
| Caelo               | Gentamicin sulfate | 12163204     | 5              |
| Caelo               | Gentamicin sulfate | 12163206     | 1              |
| Phönix Gotha        | Gentamicin sulfate | 12163207     | 1              |
| Caelo               | Gentamicin sulfate | 12163207     | 4              |
| Caelo               | Gentamicin sulfate | 12163209     | 1              |
| Fagron              | Gentamicin sulfate | 12B21-N02    | 2              |
| Fagron              | Gentamicin sulfate | 1221-n02     | 1              |
| Anzag 06.09.2012    | Gentamicin sulfate | 12D26-N05    | 1              |
| Phoenix             | Gentamicin sulfate | 12D26-N05    | 1              |
| Fagron              | Gentamicin sulfate | 12D6-N05     | 1              |
| Fagron              | Gentamicin sulfate | 12D26N05     | 1              |
| Fagron              | Gentamicin sulfate | 12g04-n16    | 1              |
| Kehr                | Gentamicin sulfate | 12G04-N16    | 1              |
| Fagron              | Gentamicin sulfate | 12G04-N16    | 1              |
| Alliance Healthcare | Gentamicin sulfate | 12G04-N16    | 1              |
| Fagron              | Gentamicin sulfate | 12117-no2    | 1              |
| Euro OTC            | Gentamicin sulfate | 130504701    | 1              |
| Caelo               | Gentamicin sulfate | 13091207     | 1              |
| Caelo               | Gentamicin sulfate | 13189602     | 6              |

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| Supplier     | Substance          | Batch       | Spectra |
|--------------|--------------------|-------------|---------|
| Phönix/Maros | Gentamicin sulfate | 13189602    | 1       |
| Caelo        | Gentamicin sulfate | 13189603    | 3       |
| Caelo        | Gentamicin sulfate | 13189605    | 1       |
| Fagron       | Gentamicin sulfate | 13189607    | 1       |
| Noweda       | Gentamicin sulfate | 13189607    | 1       |
| Caelo        | Gentamicin sulfate | 13D24-N05   | 1       |
| Caelo        | Gentamicin sulfate | 1710I-01582 | 1       |
| Fagron       | Gentamicin sulfate | 20100512-3  | 1       |
| Euro OTC     | Gentamicin sulfate | 2911034-02  | 1       |
| Caelo        | Gentamicin sulfate | 3110806     | 1       |
| Caelo        | Gentamicin sulfate | 312012      | 1       |
| Caelo        | Gentamicin sulfate | 32131-01582 | 1       |
| Caelo        | Gentamicin sulfate | 73402189    | 1       |
| EuRho        | Gentamicin sulfate | FG1112482   | 1       |
| Fargon       | Gentamicin sulfate | 13D24-N05   | 1       |
| Sanacorp     | Gentamicin sulfate | 13189607    | 1       |

- 69 059 spectra from 414 *Apo-Ident* customers from a total of 23 641 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Gentamicin sulfate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Gentamicin sulfate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 360           | 0              | 71 026        |
| <b>Type B</b> | 0              | 395           | 240            | 146 094       |
| <b>Type C</b> | 0              | 509           | 65             | 69 059        |

The substance/substance group *Gentamicin sulfate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.3333 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 62.2047 % (> 61.7323 %)  |
| <b>Type C</b> | 100.0000 % (> 99.9812 %) | 88.6760 % (> 88.1533 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.



### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20661     | 20661               | 0.00                         | 20.04                           |
| 21081     | 21837               | 6.25                         | 28.86                           |
| 21580     | 21837               | 5.99                         | 32.82                           |
| 21582     | 21582               | 0.00                         | 25.80                           |
| 21684     | 21837               | 3.08                         | 26.17                           |
| 21837     | 21837               | 0.00                         | 32.66                           |
| 22604     | 21837               | 9.96                         | 31.53                           |
| 22857     | 22857               | 0.00                         | 21.95                           |
| 23210     | 21837               | 4.88                         | 27.10                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Glucose monohydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20031-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Glucose monohydrate; Glucosum monohydricum; Saccharum amylaceum

### Special notes

When selecting the *Glucose monohydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Glucose monohydrate*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------------|-----------|-----------|---------|-------------|
| Fagron   | Glucose monohydr... | 11L19-N13 | 20799     | 40      | 20120105    |
| Fagron   | Glucose monohydr... | 14B04-B01 | 21274     | 40      | 20140304    |
| Euro OTC | Glucose monohydr... | 1509006   | 21905     | 40      | 20150914*   |
| Euro OTC | Glucose monohydr... | 1601016   | 22308     | 40      | 1601016*    |
| Euro OTC | Glucose monohydr... | 1604006   | 22538     | 40      | 20160511*   |
| Euro OTC | Glucose monohydr... | 1701002   | 23006     | 40      | 20170213*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Glucose monohydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 315 spectra of 8 reference samples from the substance/substance group *Glucose monohydrate*.

| Supplier | Substance           | Batch      | Sample ID          | Spectra |
|----------|---------------------|------------|--------------------|---------|
| Caelo    | Glucose monohydrate | 82246219   | 20031              | 75      |
| Euro OTC | Glucose monohydrate | 1210034-02 | 21285              | 40      |
| Euro OTC | Glucose monohydrate | 1509006    | 21905 <sup>†</sup> | 20      |
| Euro OTC | Glucose monohydrate | 1601016    | 22308 <sup>†</sup> | 20      |
| Euro OTC | Glucose monohydrate | 1607024    | 22692              | 40      |
| Caelo    | Glucose monohydrate | 16184807   | 23025              | 40      |
| Caelo    | Glucose monohydrate | 171368     | 23304              | 40      |
| Euro OTC | Glucose monohydrate | 1707004    | 23545              | 40      |

- 146 414 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 923 spectra from 194 *Apo-Ident* customers from 240 batches from the substance/substance group *Glucose monohydrate*.

| Supplier                   | Substance           | Batch            | Spectra |
|----------------------------|---------------------|------------------|---------|
| Noweda                     | Glucose monohydrate | 1210034          | 1       |
| EuRho                      | Glucose monohydrate | 1204044-01       | 2       |
| Caelo                      | Glucose monohydrate | 12284229         | 5       |
| Caelo                      | Glucose monohydrate | 13157007         | 8       |
| Euro OTC                   | Glucose monohydrate | 2313E-02209      | 1       |
| EuRho                      | Glucose monohydrate | 2710Q-02209      | 1       |
| Dextro Energy GmbH/Sana... | Glucose monohydrate | L1299            | 1       |
| Dextro Energy GmbH/Krie... | Glucose monohydrate |                  | 1       |
| Dextro Energy              | Glucose monohydrate | 13171            | 1       |
| Dextro EnergyGmbH          | Glucose monohydrate | L4036            | 1       |
| Dextro Energy GmbH/Gehe    | Glucose monohydrate | L4163            | 2       |
| Dextro Energy GmbH/Gehe    | Glucose monohydrate | L4164            | 1       |
| Dextro EnergyGmbH          | Glucose monohydrate | L4273            | 1       |
| Dextro GmbH/Noweda         | Glucose monohydrate | L5301            | 1       |
| Dextro Energy GmbH/Gehe    | Glucose monohydrate | L4274            | 1       |
| Fagron                     | Glucose monohydrate |                  | 1       |
| Euro OTC                   | Glucose monohydrate | 96-01            | 1       |
| Eigenherstellung           | Glucose monohydrate | 40615HJK01       | 1       |
| GATT-KOLLER/PHOENIX        | Glucose monohydrate | 243/02142614     | 1       |
| GATT-KOLLER/PHOENIX        | Glucose monohydrate | 243/02141714     | 1       |
| Caelo                      | Glucose monohydrate | 2101402          | 1       |
| Klenk                      | Glucose monohydrate | 4298924          | 1       |
| Caelo                      | Glucose monohydrate | 5051401          | 1       |
| Caelo                      | Glucose monohydrate | 11021509         | 1       |
| Euro OTC                   | Glucose monohydrate | 1103027-01       | 1       |
| Euro OTC                   | Glucose monohydrate | 1210034-02       | 8       |
| Euro OTC                   | Glucose monohydrate | 1210034-03       | 1       |
| Sanacorp                   | Glucose monohydrate | 12284230         | 1       |
| Caelo                      | Glucose monohydrate | 12284231         | 1       |
| Euro OTC                   | Glucose monohydrate | 1305030-02       | 7       |
| Klenk                      | Glucose monohydrate | 13157002         | 8       |
| Caelo                      | Glucose monohydrate | 13157002         | 4       |
| Caelo                      | Glucose monohydrate | 13157005         | 13      |
| Caelo                      | Glucose monohydrate | 13157008         | 2       |
| Caelo                      | Glucose monohydrate | 13157011         | 13      |
| Caelo                      | Glucose monohydrate | 13157012         | 1       |
| Caelo                      | Glucose monohydrate | 13157013         | 1       |
| Caelo                      | Glucose monohydrate | 13157017         | 1       |
| Caelo                      | Glucose monohydrate | 13157019         | 10      |
| Caelo                      | Glucose monohydrate | 13157026         | 3       |
| Gehe                       | Glucose monohydrate | 13157026         | 2       |
| Fagron                     | Glucose monohydrate | 13B01-N03        | 5       |
| Fagron                     | Glucose monohydrate | 13H06-N08        | 17      |
| Caelo                      | Glucose monohydrate | 13H06-N08        | 2       |
| Fagron                     | Glucose monohydrate | 13H14-B06-289483 | 1       |
| Euro OTC                   | Glucose monohydrate | 140004-01        | 1       |
| Euro OTC                   | Glucose monohydrate | 14005004-02      | 1       |
| Euro OTC                   | Glucose monohydrate | 1401019-01       | 14      |
| Phönix Gotha               | Glucose monohydrate | 1401019-01       | 1       |
| Fagron                     | Glucose monohydrate | 1401019-01       | 1       |
| gehe                       | Glucose monohydrate | 1401019-02       | 1       |
| Euro OTC                   | Glucose monohydrate | 140101902        | 2       |
| Ph.Eur.8.0                 | Glucose monohydrate | 1401019-02       | 1       |
| Euro OTC                   | Glucose monohydrate | 1401019-02       | 1       |

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| <b>Supplier</b>     | <b>Substance</b>    | <b>Batch</b>     | <b>Spectra</b> |
|---------------------|---------------------|------------------|----------------|
| Euro OTC            | Glucose monohydrate | 1405004-01       | 12             |
| Euro OTC            | Glucose monohydrate | 140500401        | 2              |
| Sonnenberg-Apotheke | Glucose monohydrate | 140500401        | 1              |
| EuRho/Phoenix       | Glucose monohydrate | 140500401        | 1              |
| Euro OTC            | Glucose monohydrate | 1405004-02       | 4              |
| Phönix Gotha        | Glucose monohydrate | 1405004-02       | 1              |
| Euro OTC            | Glucose monohydrate | 140500402        | 1              |
| Fagron              | Glucose monohydrate | 1407-808-307707  | 1              |
| Euro OTC            | Glucose monohydrate | 1410019-01       | 8              |
| Euro OTC            | Glucose monohydrate | 141001901        | 1              |
| Euro OTC            | Glucose monohydrate | 1410019-02       | 2              |
| Caelo               | Glucose monohydrate | 1410019-02       | 1              |
| Caelo               | Glucose monohydrate | 14102401         | 5              |
| AHD                 | Glucose monohydrate | 14102407         | 1              |
| Caelo               | Glucose monohydrate | 14102407         | 2              |
| Caelo               | Glucose monohydrate | 14102411         | 5              |
| Gehe                | Glucose monohydrate | 14102411         | 1              |
| Caelo               | Glucose monohydrate | 14102412         | 11             |
| Fagron              | Glucose monohydrate | 14102412         | 2              |
| Caelo               | Glucose monohydrate | 14102415         | 1              |
| Caelo               | Glucose monohydrate | 14102416         | 5              |
| Noweda 06.10.2014   | Glucose monohydrate | 14102416         | 1              |
| Caelo               | Glucose monohydrate | 14102418         | 8              |
| Gehe                | Glucose monohydrate | 14102419         | 1              |
| Caelo               | Glucose monohydrate | 14102419         | 1              |
| Caelo               | Glucose monohydrate | 14102420         | 5              |
| Caelo               | Glucose monohydrate | 14102421         | 7              |
| Caelo               | Glucose monohydrate | 14102424         | 1              |
| Caelo               | Glucose monohydrate | 14102427         | 2              |
| Caelo               | Glucose monohydrate | 14102430         | 3              |
| Caelo               | Glucose monohydrate | 14102430         | 1              |
| Caelo               | Glucose monohydrate | 14120419         | 1              |
| Caelo               | Glucose monohydrate | 14334801         | 1              |
| Caelo               | Glucose monohydrate | 14334802         | 9              |
| Noweda 10.02.2015   | Glucose monohydrate | 14334802         | 3              |
| Bombastus           | Glucose monohydrate | 14334802         | 2              |
| Caelo               | Glucose monohydrate | 14334807         | 3              |
| Caelo               | Glucose monohydrate | 14334809         | 1              |
| Caelo               | Glucose monohydrate | 14334808         | 2              |
| Caelo               | Glucose monohydrate | 14334810         | 6              |
| Caelo               | Glucose monohydrate | 14334811         | 2              |
| Caelo               | Glucose monohydrate | 14334812         | 1              |
| Fagron              | Glucose monohydrate | 14B04-B01        | 3              |
| Euro OTC            | Glucose monohydrate | 145004-01        | 1              |
| Fagron              | Glucose monohydrate | 14B04-B01-291137 | 6              |
| Caelo               | Glucose monohydrate | 14B04-B01-291137 | 1              |
| Fagron              | Glucose monohydrate | 14B04-B01-291138 | 1              |
| Fagron              | Glucose monohydrate | 14B04-B01-291143 | 2              |
| Fagron              | Glucose monohydrate | 14B28-B02        | 4              |
| Fagron              | Glucose monohydrate | 14B28-B02-291353 | 10             |
| Fagron              | Glucose monohydrate | 14B28-B02-291354 | 4              |
| Fagron              | Glucose monohydrate | 14I04-B08        | 1              |
| Caelo               | Glucose monohydrate |                  | 3              |
| Caelo               | Glucose monohydrate | 14I04-B08        | 4              |
| Fagron              | Glucose monohydrate | 14I04-B08-298602 | 3              |
| Fagron              | Glucose monohydrate | 14I04B8298602    | 1              |
| Euro OTC            | Glucose monohydrate | 1504028-01       | 11             |
| Euro/ Sanacorp      | Glucose monohydrate | 1504028-01       | 1              |
| Euro OTC            | Glucose monohydrate | 150402801        | 1              |
| Euro OTC            | Glucose monohydrate | 1504028-02       | 5              |

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| Supplier                 | Substance           | Batch            | Spectra |
|--------------------------|---------------------|------------------|---------|
| Euro OTC                 | Glucose monohydrate | 15040281         | 1       |
| Euro OTC                 | Glucose monohydrate | 1509006-01       | 13      |
| Euro OTC                 | Glucose monohydrate | 150900601        | 1       |
| Euro OTC                 | Glucose monohydrate | 1509006-02       | 3       |
| Caelo                    | Glucose monohydrate | 15095601         | 16      |
| Euro OTC                 | Glucose monohydrate | 1509006-1        | 1       |
| Euro OTC                 | Glucose monohydrate | 15095601         | 1       |
| Caelo                    | Glucose monohydrate | 15095602         | 1       |
| Caelo                    | Glucose monohydrate | 15095603         | 1       |
| Caelo                    | Glucose monohydrate | 15095605         | 3       |
| Caelo                    | Glucose monohydrate | 15095611         | 2       |
| Caelo                    | Glucose monohydrate | 15095612         | 10      |
| Noweda 30.07.2015        | Glucose monohydrate | 15095612         | 1       |
| Caelo                    | Glucose monohydrate | 15180001         | 11      |
| Caelo                    | Glucose monohydrate | 15180002         | 13      |
| Caelo                    | Glucose monohydrate | 15180003         | 3       |
| Euro OTC                 | Glucose monohydrate | 15180010         | 1       |
| Caelo                    | Glucose monohydrate | 15180010         | 3       |
| Caelo                    | Glucose monohydrate | 15180005         | 3       |
| Caelo                    | Glucose monohydrate | 15180012         | 21      |
| Caelo                    | Glucose monohydrate | 15180013         | 3       |
| Caesar & Loretz GmbH     | Glucose monohydrate | 15180013         | 1       |
| Caelo                    | Glucose monohydrate | 15180015         | 7       |
| Caelo                    | Glucose monohydrate | 15180016         | 1       |
| Caelo                    | Glucose monohydrate | 1518002          | 1       |
| Fagron                   | Glucose monohydrate | 1521-B06-309508  | 1       |
| Caecolo/Noweda           | Glucose monohydrate | 15413301         | 1       |
| Caelo                    | Glucose monohydrate | 15413302         | 4       |
| Caelo                    | Glucose monohydrate | 15413303         | 1       |
| Caelo                    | Glucose monohydrate | 15413304         | 24      |
| Noweda 10.032016         | Glucose monohydrate | 15413304         | 2       |
| Caesa/Phoenix            | Glucose monohydrate | 15413304         | 1       |
| Caelo                    | Glucose monohydrate | 15413401         | 5       |
| Caelo                    | Glucose monohydrate | 15413402         | 3       |
| Caesar & Loretz GmbH     | Glucose monohydrate | 15413402         | 1       |
| Caelo                    | Glucose monohydrate | 15413405         | 2       |
| Caelo                    | Glucose monohydrate | 15413409         | 18      |
| Caelo                    | Glucose monohydrate | 15413410         | 3       |
| Bombastus                | Glucose monohydrate | 15413410         | 1       |
| Caelo                    | Glucose monohydrate | 15413412         | 1       |
| Caelo/ Noweda            | Glucose monohydrate | 15413412         | 1       |
| Fagron                   | Glucose monohydrate | 15A21-B06-309508 | 3       |
| Fagron                   | Glucose monohydrate | 15B01291137      | 1       |
| Euro OTC                 | Glucose monohydrate | 1601016-01       | 13      |
| Euro OTC                 | Glucose monohydrate | 1601016-02       | 3       |
| Euro OTC                 | Glucose monohydrate | 16040060-01      | 1       |
| Euroo                    | Glucose monohydrate | 1604006-01       | 1       |
| Euro OTC                 | Glucose monohydrate | 1604006-01       | 8       |
| Euro/Alliance Healthcare | Glucose monohydrate | 1604006-01       | 1       |
| Euro OTC                 | Glucose monohydrate | 1604006-02       | 10      |
| Euro/Noweda              | Glucose monohydrate | 1604006-02       | 2       |
| Caelo                    | Glucose monohydrate | 16049101         | 13      |
| Caelo                    | Glucose monohydrate | 16049102         | 5       |
| Caesar & Loretz/Noweda   | Glucose monohydrate | 16049102         | 1       |
| Caelo                    | Glucose monohydrate | 16049103         | 1       |
| Caelo                    | Glucose monohydrate | 16049104         | 7       |
| Caelo                    | Glucose monohydrate | 16049105         | 5       |
| Euro OTC                 | Glucose monohydrate | 1607024-01       | 3       |
| Euro OTC                 | Glucose monohydrate | 1607024-02       | 5       |
| Eigenherstellung         | Glucose monohydrate | 160915HML01      | 1       |

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| <b>Supplier</b>            | <b>Substance</b>    | <b>Batch</b> | <b>Spectra</b> |
|----------------------------|---------------------|--------------|----------------|
| Caelo                      | Glucose monohydrate | 16184801     | 8              |
| Caelo                      | Glucose monohydrate | 16184802     | 1              |
| Caelo                      | Glucose monohydrate | 16184807     | 2              |
| Caelo                      | Glucose monohydrate | 16184808     | 3              |
| Caelo                      | Glucose monohydrate | 16184810     | 7              |
| Caelo                      | Glucose monohydrate | 16184816     | 1              |
| Caelo                      | Glucose monohydrate | 17136802     | 1              |
| Caelo                      | Glucose monohydrate | 17005801     | 1              |
| Caelo                      | Glucose monohydrate | 17005802     | 2              |
| Caelo                      | Glucose monohydrate | 17005803     | 5              |
| Caelo                      | Glucose monohydrate | 17005804     | 2              |
| Euro OTC                   | Glucose monohydrate | 1701002-01   | 8              |
| Apotheke im Forum          | Glucose monohydrate | 17010002-01  | 1              |
| Caelo                      | Glucose monohydrate | 17005811     | 1              |
| Caelo                      | Glucose monohydrate | 18071402     | 1              |
| Caelo                      | Glucose monohydrate | 200415PJK01  | 1              |
| Caelo                      | Glucose monohydrate | 28051507     | 1              |
| Caelo                      | Glucose monohydrate | 2316E-02209  | 1              |
| Caelo                      | Glucose monohydrate | 613011-3p    | 1              |
| Caelo                      | Glucose monohydrate | 5092         | 1              |
| Caelo                      | Glucose monohydrate | E056D        | 1              |
| Fagron                     | Glucose monohydrate | EOAJ5        | 1              |
| Fagron                     | Glucose monohydrate | E144C        | 3              |
| Eigenherstellung           | Glucose monohydrate | 30912HML01   | 1              |
| Fagron                     | Glucose monohydrate | 8G31-N09     | 1              |
| Noweda                     | Glucose monohydrate | 10082017     | 1              |
| Bombastus                  | Glucose monohydrate | 1103027-01   | 1              |
| Euro OTC                   | Glucose monohydrate | 1108061-01   | 1              |
| Eurho/Sanacorp             | Glucose monohydrate | 1108061-01   | 2              |
| Caelo                      | Glucose monohydrate | 1108061-01   | 1              |
| EuRho                      | Glucose monohydrate | 1108061-01   | 1              |
| Gehe                       | Glucose monohydrate | 1108061-01   | 1              |
| Noweda                     | Glucose monohydrate | 1108061-01   | 1              |
| Euro OTC                   | Glucose monohydrate | 1108061-02   | 3              |
| EuRho                      | Glucose monohydrate | 1108061-02   | 1              |
| Caelo                      | Glucose monohydrate | 11082014     | 1              |
| Caelo                      | Glucose monohydrate | 11082020     | 2              |
| Eigenherstellung           | Glucose monohydrate | 110912HML01  | 1              |
| Eigenherstellung           | Glucose monohydrate | 110913HJK02  | 1              |
| Euro OTC                   | Glucose monohydrate | 1114U2209    | 1              |
| Caelo                      | Glucose monohydrate | 1131416      | 1              |
| Caelo                      | Glucose monohydrate | 11314516     | 6              |
| Caelo                      | Glucose monohydrate | 11314519     | 2              |
| Caelo                      | Glucose monohydrate | 11314521     | 1              |
| Caelo                      | Glucose monohydrate | 11314525     | 1              |
| Caelo                      | Glucose monohydrate | 11314526     | 1              |
| Caelo                      | Glucose monohydrate | 11314528     | 11             |
| Noweda                     | Glucose monohydrate | 11B22-N06    | 1              |
| Noweda                     | Glucose monohydrate | 11K16-N01    | 1              |
| Caelo                      | Glucose monohydrate | 11L19-N13    | 3              |
| Fagron                     | Glucose monohydrate | 11L19-N13    | 1              |
| Euro OTC                   | Glucose monohydrate | 1204044-01   | 3              |
| Noweda                     | Glucose monohydrate | 1204044-01   | 3              |
| Euro OTC                   | Glucose monohydrate | 1204044-02   | 10             |
| Gehe                       | Glucose monohydrate | 1204044-02   | 3              |
| Eigenherstellung           | Glucose monohydrate | 120912HML02  | 1              |
| Euro OTC                   | Glucose monohydrate | 1210034-01   | 10             |
| Gehe                       | Glucose monohydrate | 1210034-01   | 5              |
| Fagron                     | Glucose monohydrate | 1210034-01   | 1              |
| Roquette Lestrem FR/ No... | Glucose monohydrate | 1210034-02   | 1              |

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| Supplier               | Substance           | Batch       | Spectra |
|------------------------|---------------------|-------------|---------|
| Caelo                  | Glucose monohydrate | 1210034-02  | 1       |
| Gehe                   | Glucose monohydrate | 1210034-02  | 1       |
| Caelo                  | Glucose monohydrate | 12284202    | 9       |
| Caelo                  | Glucose monohydrate | 12284204    | 2       |
| Caelo                  | Glucose monohydrate | 12284206    | 7       |
| Anzag 04.04.13         | Glucose monohydrate | 12284206    | 1       |
| Phoenix                | Glucose monohydrate | 12284206    | 1       |
| Caelo                  | Glucose monohydrate | 12284210    | 2       |
| Caelo                  | Glucose monohydrate | 12284219    | 11      |
| Caelo                  | Glucose monohydrate | 12284222    | 3       |
| Caelo                  | Glucose monohydrate | 12284230    | 5       |
| Fagron                 | Glucose monohydrate | 12B09-N05   | 1       |
| Kehr                   | Glucose monohydrate | 12C26-N06   | 1       |
| Fagron                 | Glucose monohydrate | 12G30-N01   | 10      |
| Noweda                 | Glucose monohydrate | 12G30-N01   | 3       |
| Anzag                  | Glucose monohydrate | 12G30-N01   | 1       |
| Caelo                  | Glucose monohydrate | 12G30-N01   | 1       |
| Caelo                  | Glucose monohydrate | 12G30-N001  | 1       |
| Fagron                 | Glucose monohydrate | 12G30-N01   | 2       |
| Euro OTC               | Glucose monohydrate | 1305030     | 1       |
| Euro OTC               | Glucose monohydrate | 1305030-01  | 7       |
| Euro OTC               | Glucose monohydrate | 130503001   | 1       |
| Caelo                  | Glucose monohydrate | 1305030-02  | 1       |
| Gehe                   | Glucose monohydrate | 130503002   | 1       |
| Euro OTC               | Glucose monohydrate | 1305030-02  | 1       |
| Fagron                 | Glucose monohydrate | 13AN01      | 1       |
| Caelo                  | Glucose monohydrate | 13157022    | 1       |
| Fagron                 | Glucose monohydrate | 13A25-N01   | 12      |
| Fargron                | Glucose monohydrate | 13A25-N01   | 1       |
| Fagron                 | Glucose monohydrate | 13A25-n01   | 1       |
| Fagron                 | Glucose monohydrate | 13A25-No1   | 1       |
| Fagron                 | Glucose monohydrate | 13A25-N01   | 2       |
| Fagron                 | Glucose monohydrate | 13B01N03    | 1       |
| Caelo                  | Glucose monohydrate | 13B01-N03   | 1       |
| FARGON                 | Glucose monohydrate | 13b01-n03   | 1       |
| Fagron                 | Glucose monohydrate | 13C25N09    | 2       |
| Fagron                 | Glucose monohydrate | 13C25-N09   | 8       |
| Fargon                 | Glucose monohydrate | 13C25-N09   | 1       |
| Fagron                 | Glucose monohydrate | 13C25-N09   | 1       |
| pharma gmbh            | Glucose monohydrate | 1401019-01  | 1       |
| Euro OTC               | Glucose monohydrate | 140101901   | 1       |
| Euro OTC               | Glucose monohydrate | 1406212209  | 1       |
| Phönix                 | Glucose monohydrate | 1504028-01  | 1       |
| EuRho                  | Glucose monohydrate | 151780      | 1       |
| Fagron                 | Glucose monohydrate | 151780-0004 | 1       |
| Euro OTC               | Glucose monohydrate | 1601312209  | 1       |
| Eigenherstellung       | Glucose monohydrate | 180213HJK01 | 1       |
| Euro OTC               | Glucose monohydrate | 2013U-02209 | 1       |
| Euro OTC               | Glucose monohydrate | 2023012-1   | 1       |
| Fagron                 | Glucose monohydrate | 270313PML01 | 1       |
| Euro OTC               | Glucose monohydrate | 31102013B   | 1       |
| Fagron                 | Glucose monohydrate | 3413E-02209 | 1       |
| Euro OTC               | Glucose monohydrate | 3413Q-02209 | 1       |
| Fagron                 | Glucose monohydrate | 4213Q-02209 | 1       |
| Euro OTC               | Glucose monohydrate | E267X       | 1       |
| Caelo                  | Glucose monohydrate | E144C       | 1       |
| Fagron                 | Glucose monohydrate | E368B       | 1       |
| Fagron                 | Glucose monohydrate | E524W       | 1       |
| Fagron                 | Glucose monohydrate | E571X       | 2       |
| dextro energy / Noweda | Glucose monohydrate | L1299       | 1       |

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| Supplier                   | Substance           | Batch      | Spectra |
|----------------------------|---------------------|------------|---------|
| Dextro/Krieger/15.05.13    | Glucose monohydrate | 13092      | 1       |
| Caelo                      | Glucose monohydrate | 14334805   | 2       |
| Caelo                      | Glucose monohydrate | 15095606   | 1       |
| Caelo                      | Glucose monohydrate | 1134506    | 1       |
| Caelo                      | Glucose monohydrate | 16049107   | 1       |
| Sanacorp,30.03.17, 7,12EUR | Glucose monohydrate | 16184810   | 1       |
| Fagron                     | Glucose monohydrate | 11K16-N01  | 1       |
| Gutenberg-Apotheke         | Glucose monohydrate | 14B04-B01  | 1       |
| Caesar & Lorenz            | Glucose monohydrate | 13157007   | 1       |
| Fragon                     | Glucose monohydrate | 13H06-N08  | 1       |
| Caelo                      | Glucose monohydrate | 13157021   | 1       |
| Phönix                     | Glucose monohydrate | 1401019-01 | 1       |
| Caelo                      | Glucose monohydrate | 1401019-01 | 1       |
| Sanacorp                   | Glucose monohydrate | 3/AKD100   | 1       |
| Dextro Energy              | Glucose monohydrate | L3270      | 1       |
| Phönix                     | Glucose monohydrate | 1210334-02 | 1       |
| Caelo                      | Glucose monohydrate | 13A25-N01  | 5       |
| Dextro                     | Glucose monohydrate | L0222      | 1       |

- 68 710 spectra from 414 *Apo-Ident* customers from a total of 23 566 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Glucose monohydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Glucose monohydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 315           | 0              | 146 414       |
| <b>Type C</b> | 0              | 906           | 17             | 68 710        |

The substance/substance group *Glucose monohydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.0952 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 98.1582 % (> 97.8332 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.



### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20799     | 21905               | 3.34                         | 33.01                           |
| 21274     | 21905               | 3.56                         | 26.30                           |
| 21905     | 21905               | 0.00                         | 28.59                           |
| 22308     | 22308               | 0.00                         | 24.99                           |
| 22538     | 22538               | 0.00                         | 32.19                           |
| 23006     | 23006               | 0.00                         | 26.29                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Glucose, anhydrous**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20982-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Glucose, anhydrous; Glucosum anhydricum; Saccharum amylaceum anhydricum

### Special notes

When selecting the *Glucose, anhydrous* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Glucose, anhydrous*:

| Supplier | Substance          | Batch    | Sample ID | Spectra | Certificate |
|----------|--------------------|----------|-----------|---------|-------------|
| Caelo    | Glucose, anhydrous | 12294514 | 20982     | 40      | 1402475     |
| Caelo    | Glucose, anhydrous | 14033901 | 21363     | 40      | 20140214    |
| Caelo    | Glucose, anhydrous | 14142310 | 21703     | 30      | 20140523    |
| Caelo    | Glucose, anhydrous | 16050501 | 22586     | 40      | 20160317    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 150 spectra of 4 reference samples from the substance/substance group *Glucose, anhydrous*. These samples are listed above in the [calibration samples](#) section.
- 71 236 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 125 spectra of 4 reference samples from the substance/substance group *Glucose, anhydrous*.

| Supplier | Substance          | Batch    | Sample ID          | Spectra |
|----------|--------------------|----------|--------------------|---------|
| Caelo    | Glucose, anhydrous | 11017101 | 20262              | 30      |
| Caelo    | Glucose, anhydrous | 11017110 | 20279              | 40      |
| Caelo    | Glucose, anhydrous | 14142310 | 21703 <sup>†</sup> | 15      |
| Caelo    | Glucose, anhydrous | 16157401 | 23583              | 40      |

- 146 604 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 305 spectra from 69 *Apo-Ident* customers from 130 batches from the substance/substance group *Glucose, anhydrous*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                   | Substance          | Batch       | Spectra |
|----------------------------|--------------------|-------------|---------|
| Caelo                      | Glucose, anhydrous | 4071505     | 1       |
| Caelo                      | Glucose, anhydrous | 3121402     | 1       |
| Caelo                      | Glucose, anhydrous | 5081401     | 1       |
| Caelo                      | Glucose, anhydrous | 6031505     | 1       |
| Caelo                      | Glucose, anhydrous | 10091503    | 1       |
| Caelo                      | Glucose, anhydrous | 13178712    | 1       |
| Caelo                      | Glucose, anhydrous | 13041501    | 1       |
| GEHE                       | Glucose, anhydrous | 13178715    | 1       |
| Caelo                      | Glucose, anhydrous | 13329503    | 2       |
| Caelo                      | Glucose, anhydrous | 13329512    | 6       |
| PHOENIX 30.05.2014         | Glucose, anhydrous | 13329514    | 1       |
| Caelo                      | Glucose, anhydrous | 14033901    | 2       |
| Gehe                       | Glucose, anhydrous | 14033901    | 1       |
| Caelo                      | Glucose, anhydrous | 14033902    | 5       |
| Caelo                      | Glucose, anhydrous | 14033906    | 5       |
| Caelo                      | Glucose, anhydrous | 14033907    | 5       |
| GEHE 17.07.2014            | Glucose, anhydrous | 14033907    | 1       |
| AHD                        | Glucose, anhydrous | 14033908    | 1       |
| Caelo                      | Glucose, anhydrous | 14033908    | 2       |
| Caelo                      | Glucose, anhydrous | 14051401    | 1       |
| Caelo                      | Glucose, anhydrous | 14142301    | 2       |
| Fagron                     | Glucose, anhydrous | 14142303    | 1       |
| Caelo                      | Glucose, anhydrous | 14142303    | 2       |
| Caelo                      | Glucose, anhydrous | 14142308    | 1       |
| Phoenix 27.11.2014         | Glucose, anhydrous | 14142303    | 2       |
| Caelo                      | Glucose, anhydrous | 14142304    | 1       |
| Gehe 27.11.14              | Glucose, anhydrous | 14142309    | 1       |
| Caelo                      | Glucose, anhydrous | 14142310    | 3       |
| Caelo                      | Glucose, anhydrous | 14142313    | 2       |
| Phoenix                    | Glucose, anhydrous | 14142310    | 1       |
| Gehe Kassel                | Glucose, anhydrous | 14142313    | 1       |
| Caelo                      | Glucose, anhydrous | 14142314    | 3       |
| Caelo                      | Glucose, anhydrous | 1415U-03393 | 1       |
| Caelo                      | Glucose, anhydrous | 14319302    | 1       |
| Caelo                      | Glucose, anhydrous | 14319304    | 6       |
| Caelo                      | Glucose, anhydrous | 14319308    | 1       |
| Caelo                      | Glucose, anhydrous | 14319309    | 4       |
| Gehe Kassel                | Glucose, anhydrous | 14319310    | 1       |
| Caelo                      | Glucose, anhydrous | 14319310    | 2       |
| Caelo                      | Glucose, anhydrous | 1439304     | 1       |
| Caelo                      | Glucose, anhydrous | 15095001    | 7       |
| Caelo                      | Glucose, anhydrous | 15095004    | 2       |
| Caelo                      | Glucose, anhydrous | 15148801    | 2       |
| Caelo                      | Glucose, anhydrous | 15148802    | 4       |
| Phoenix                    | Glucose, anhydrous | 15148801    | 1       |
| Caelo                      | Glucose, anhydrous | 15095005    | 2       |
| Caelo                      | Glucose, anhydrous | 15148803    | 1       |
| Caelo                      | Glucose, anhydrous | 15148807    | 5       |
| Caelo                      | Glucose, anhydrous | 15148808    | 3       |
| Euro OTC                   | Glucose, anhydrous | 15148808    | 1       |
| Caelo                      | Glucose, anhydrous | 15148810    | 4       |
| Caelo                      | Glucose, anhydrous | 15148809    | 1       |
| Caelo                      | Glucose, anhydrous | 15148813    | 1       |
| Caesar & Loretz GmbH Hi... | Glucose, anhydrous | 15321906    | 1       |
| Caelo                      | Glucose, anhydrous | 15329001    | 5       |
| Rondell Apotheke           | Glucose, anhydrous | 15329003    | 1       |
| Caelo                      | Glucose, anhydrous | 15329004    | 4       |
| Fagron                     | Glucose, anhydrous | 15329005    | 2       |
| Caelo                      | Glucose, anhydrous | 15329005    | 3       |
| Caelo                      | Glucose, anhydrous | 15329006    | 3       |

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| Supplier                     | Substance          | Batch       | Spectra |
|------------------------------|--------------------|-------------|---------|
| Caesar & Loretz GmbH Hi. . . | Glucose, anhydrous | 15329006    | 1       |
| Caelo                        | Glucose, anhydrous | 15329008    | 1       |
| Phoenix                      | Glucose, anhydrous | 15329010    | 2       |
| Caelo                        | Glucose, anhydrous | 16050501    | 8       |
| Caelo                        | Glucose, anhydrous | 16050502    | 2       |
| Klenk                        | Glucose, anhydrous | 16050502    | 1       |
| Caelo                        | Glucose, anhydrous | 16050503    | 4       |
| Phoenix                      | Glucose, anhydrous | 16050503    | 4       |
| Caelo                        | Glucose, anhydrous | 16050504    | 1       |
| Allianc. Healthc. /c         | Glucose, anhydrous | 16050510    | 1       |
| Caelo                        | Glucose, anhydrous | 16050510    | 1       |
| Caelo                        | Glucose, anhydrous | 1614U3393   | 1       |
| Caelo                        | Glucose, anhydrous | 16157403    | 13      |
| Gehe                         | Glucose, anhydrous | 16157403    | 2       |
| Caelo                        | Glucose, anhydrous | 16157406    | 8       |
| Caelo                        | Glucose, anhydrous | 16157411    | 3       |
| Caelo                        | Glucose, anhydrous | 16328801    | 4       |
| Caelo                        | Glucose, anhydrous | 1650502     | 1       |
| Caelo                        | Glucose, anhydrous | 16328805    | 1       |
| Sonnen-Apotheke Wefensl. . . | Glucose, anhydrous | 17/16       | 1       |
| Apotheke-SiO2-Mischung       | Glucose, anhydrous | 18/15       | 1       |
| Caelo                        | Glucose, anhydrous | 1914I03393  | 1       |
| Caelo                        | Glucose, anhydrous | 3214M-03393 | 1       |
| Sonnen-Apotheke Wefensl. . . | Glucose, anhydrous | 34/16       | 1       |
| Caelo                        | Glucose, anhydrous | 106213393   | 1       |
| Caelo                        | Glucose, anhydrous | 402313393   | 2       |
| Caelo                        | Glucose, anhydrous | 208223393   | 1       |
| Caelo                        | Glucose, anhydrous | 214U-03393  | 1       |
| Caelo                        | Glucose, anhydrous | 712213393   | 1       |
| Caelo                        | Glucose, anhydrous | 1001313393  | 1       |
| Caelo                        | Glucose, anhydrous | 11017108    | 1       |
| Caelo                        | Glucose, anhydrous | 1114A03393  | 1       |
| Caelo                        | Glucose, anhydrous | 11017121    | 1       |
| Caelo                        | Glucose, anhydrous | 11358813    | 1       |
| Caelo                        | Glucose, anhydrous | 11358818    | 2       |
| Anzag 11.08.2012             | Glucose, anhydrous | 11358823    | 1       |
| Caelo                        | Glucose, anhydrous | 11358823    | 1       |
| Caelo                        | Glucose, anhydrous | 11358825    | 1       |
| Caelo                        | Glucose, anhydrous | 12141701    | 1       |
| Jenne                        | Glucose, anhydrous | 12141705    | 1       |
| Caelo                        | Glucose, anhydrous | 12141706    | 4       |
| Caelo                        | Glucose, anhydrous | 12141711    | 1       |
| Phönix, 02.11.2012           | Glucose, anhydrous | 12141711    | 1       |
| Caelo                        | Glucose, anhydrous | 12141714    | 2       |
| Caelo                        | Glucose, anhydrous | 12141715    | 1       |
| Phönix 04.01.13              | Glucose, anhydrous | 12141715    | 4       |
| Caelo                        | Glucose, anhydrous | 12141717    | 1       |
| Synopharm am 10.09.2012      | Glucose, anhydrous | 12141717    | 1       |
| Caelo                        | Glucose, anhydrous | 12141718    | 3       |
| Gehe 02.07.2013              | Glucose, anhydrous | 1224517     | 1       |
| Caelo                        | Glucose, anhydrous | 12294505    | 3       |
| Caelo                        | Glucose, anhydrous | 12294509    | 3       |
| Sanacorp                     | Glucose, anhydrous | 12294509    | 1       |
| Caesar&loretz,Anzag          | Glucose, anhydrous | 12294509    | 1       |
| Caelo                        | Glucose, anhydrous | 12294510    | 3       |
| Caelo                        | Glucose, anhydrous | 12294514    | 1       |
| Caelo                        | Glucose, anhydrous | 12294515    | 2       |
| Gehe 02.07.2013              | Glucose, anhydrous | 12294515    | 2       |
| Phoenix                      | Glucose, anhydrous | 12294517    | 1       |
| Caelo                        | Glucose, anhydrous | 12294517    | 2       |

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| Supplier                   | Substance          | Batch               | Spectra |
|----------------------------|--------------------|---------------------|---------|
| Caelo                      | Glucose, anhydrous | 12294519            | 1       |
| Caelo                      | Glucose, anhydrous | 1317815             | 1       |
| Phönix                     | Glucose, anhydrous | 13178701            | 1       |
| Caelo                      | Glucose, anhydrous | 13178702            | 2       |
| Caelo                      | Glucose, anhydrous | 13178704            | 4       |
| Caelo                      | Glucose, anhydrous | 13178707            | 2       |
| Caelo                      | Glucose, anhydrous | 13178711            | 3       |
| Caelo                      | Glucose, anhydrous | 13178715            | 4       |
| Caelo                      | Glucose, anhydrous | 13178716            | 1       |
| Fagron                     | Glucose, anhydrous | 13178716            | 1       |
| Caelo                      | Glucose, anhydrous | 13178718            | 1       |
| Caelo                      | Glucose, anhydrous | 13329501            | 3       |
| Caelo                      | Glucose, anhydrous | 13329504            | 2       |
| Anzag                      | Glucose, anhydrous | 13329505            | 1       |
| Caelo                      | Glucose, anhydrous | 13329507            | 2       |
| Caelo                      | Glucose, anhydrous | 15051301            | 1       |
| Caelo                      | Glucose, anhydrous | 1603213393          | 1       |
| Caelo                      | Glucose, anhydrous | 16101204            | 1       |
| Caelo                      | Glucose, anhydrous | 16101205            | 1       |
| Caelo                      | Glucose, anhydrous | 2102201301          | 1       |
| Caelo                      | Glucose, anhydrous | 4313Q3393           | 1       |
| Caelo                      | Glucose, anhydrous | 2513M03393          | 1       |
| Caelo                      | Glucose, anhydrous | 25061204            | 1       |
| Caelo                      | Glucose, anhydrous | 26041303            | 1       |
| Caelo                      | Glucose, anhydrous | 3513I-03393         | 1       |
| Caelo                      | Glucose, anhydrous | 47131-03393         | 1       |
| Caelo                      | Glucose, anhydrous | 5013I3393           | 1       |
| Caelo                      | Glucose, anhydrous | AKD14               | 1       |
| Caelo                      | Glucose, anhydrous | Glucose1            | 1       |
| Caelo                      | Glucose, anhydrous | Glucose2            | 1       |
| Caelo                      | Glucose, anhydrous | 15095003            | 2       |
| Caelo                      | Glucose, anhydrous | 12294509-3425311150 | 1       |
| PHOENIX 30.05.2014         | Glucose, anhydrous | 14033902            | 1       |
| Caelo                      | Glucose, anhydrous | 15329002            | 1       |
| Phoenix                    | Glucose, anhydrous | 16050501            | 1       |
| GEHE                       | Glucose, anhydrous | 16157406            | 1       |
| Caelo                      | Glucose, anhydrous | 23091401            | 1       |
| Apotheke/Defektur Misch... | Glucose, anhydrous |                     | 1       |
| Caelo                      | Glucose, anhydrous | 2013Q-03393         | 1       |
| Caelo                      | Glucose, anhydrous | 12141705            | 1       |

- 69 328 spectra from 414 *Apo-Ident* customers from a total of 23 672 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Glucose, anhydrous* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Glucose, anhydrous* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 150           | 0              | 71 236        |
| Type B | 0              | 114           | 11             | 146 604       |
| Type C | 0              | 281           | 24             | 69 328        |

The substance/substance group *Glucose, anhydrous* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 91.2000 % (> 88.8000 %)  |
| Type C | 100.0000 % (> 99.8812 %) | 92.1311 % (> 91.1475 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20982     | 20982               | 0.00                         | 35.25                           |
| 21363     | 20982               | 5.20                         | 35.83                           |
| 21703     | 20982               | 5.76                         | 35.80                           |
| 22586     | 20982               | 8.14                         | 34.96                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Glutamic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20436-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Glutamic acid; Acidum glutamicum; Acidum glutaminicum

### Special notes

When selecting the *Glutamic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Glutamic acid*:

| Supplier | Substance     | Batch       | Sample ID | Spectra | Certificate        |
|----------|---------------|-------------|-----------|---------|--------------------|
| Fagron   | Glutamic acid | 11I30-N02   | 20840     | 40      | AR-15-FG-010446-02 |
| Euro OTC | Glutamic acid | L1405023-01 | 21720     | 40      | 20140627           |
| Euro OTC | Glutamic acid | 1604056     | 22562     | 40      | 20160523*          |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Glutamic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Glutamic acid*.

| Supplier    | Substance     | Batch            | Sample ID          | Spectra |
|-------------|---------------|------------------|--------------------|---------|
| Pharmorgana | Glutamic acid | 1000110813       | 20436              | 40      |
| Euro OTC    | Glutamic acid | L1211001-01      | 21282              | 40      |
| Euro OTC    | Glutamic acid | L1405023-01      | 21720 <sup>†</sup> | 20      |
| Fagron      | Glutamic acid | 15G31-B08-311884 | 23599              | 40      |

- 146 589 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 9 spectra from 2 *Apo-Ident* customers from 6 batches from the substance/substance group *Glutamic acid*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance     | Batch      | Spectra |
|----------|---------------|------------|---------|
| Fagron   | Glutamic acid | 13J21-N10  | 2       |
| Euro OTC | Glutamic acid | 28071505   | 1       |
| Fagron   | Glutamic acid | 6120       | 1       |
| Fagron   | Glutamic acid | 3031502    | 1       |
| Fagron   | Glutamic acid | 13G15-N06  | 3       |
| Euro OTC | Glutamic acid | WE11020045 | 1       |

- 69 624 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Glutamic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Glutamic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 100           | 40             | 146 589       |
| <b>Type C</b> | 0              | 7             | 2              | 69 624        |

The substance/substance group *Glutamic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 71.4286 % (> 69.2857 %)  |
| <b>Type C</b> | 100.0000 % (> 99.9814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20840     | 20840               | 0.00                         | 46.09                           |
| 21720     | 22562               | 11.59                        | 50.42                           |
| 22562     | 22562               | 0.00                         | 50.96                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Glutamine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 23150-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Glutamine; Glutaminum; L-glutamine

### Special notes

When selecting the *Glutamine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Glutamine*:

| Supplier | Substance | Batch   | Sample ID | Spectra | Certificate |
|----------|-----------|---------|-----------|---------|-------------|
| Euro OTC | Glutamine | 1702007 | 23150     | 40      | 20170322*   |
| Euro OTC | Glutamine | 1706010 | 23543     | 40      | 20170802*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Glutamine*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *Glutamine*.

| Supplier | Substance | Batch            | Sample ID | Spectra |
|----------|-----------|------------------|-----------|---------|
| Fagron   | Glutamine | 17E05-B06-334869 | 23415     | 40      |
| Fagron   | Glutamine | 17E05-B06-334869 | 23416     | 40      |

- 146 649 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Glutamine*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Glutamine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Glutamine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Glutamine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 23150     | 23150               | 0.00                         | 31.34                           |
| 23543     | 23543               | 0.00                         | 30.96                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Glycine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20823-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Glycine; Glycinum

### Special notes

When selecting the *Glycine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Glycine*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate        |
|----------|-----------|------------|-----------|---------|--------------------|
| Fagron   | Glycine   | 12G13-N04  | 20823     | 40      | 1401163            |
| Fagron   | Glycine   | 13G09-N03  | 21276     | 40      | 20120711           |
| Euro OTC | Glycine   | 1402022-01 | 21534     | 40      | AR-15-FG-005430-01 |
| Caelo    | Glycine   | 13157303   | 21687     | 40      | 20130625           |
| Caelo    | Glycine   | 14147006   | 21818     | 40      | AR-16-FG-012263-01 |
| Caelo    | Glycine   | 15262518   | 23124     | 40      | 20150910           |
| Caelo    | Glycine   | 170265     | 23295     | 40      | 20170315*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 280 spectra of 7 reference samples from the substance/substance group *Glycine*. These samples are listed above in the [calibration samples](#) section.
- 71 106 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 6 reference samples from the substance/substance group *Glycine*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Euro OTC | Glycine   | 1402022-01 | 21284              | 40      |
| Euro OTC | Glycine   | 1402022-01 | 21534 <sup>†</sup> | 20      |
| Caelo    | Glycine   | 13157303   | 21687 <sup>†</sup> | 20      |
| Caelo    | Glycine   | 14147006   | 21818 <sup>†</sup> | 20      |
| Euro OTC | Glycine   | 1605035    | 22683              | 40      |
| Euro OTC | Glycine   | 1704015    | 23387              | 40      |

- 146 549 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 5 spectra from 2 *Apo-Ident* customers from 4 batches from the substance/substance group *Glycine*.

| Supplier | Substance | Batch    | Spectra |
|----------|-----------|----------|---------|
| Caelo    | Glycine   | 14147005 | 1       |
| Caelo    | Glycine   | 15262502 | 2       |
| Caelo    | Glycine   | 15262504 | 1       |
| Caelo    | Glycine   | 15262518 | 1       |

- 69 628 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Glycine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Glycine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 272           | 8              | 71 106        |
| <b>Type B</b> | 0              | 172           | 8              | 146 549       |
| <b>Type C</b> | 0              | 4             | 1              | 69 628        |

The substance/substance group *Glycine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate        |
|---------------|--------------------------|-------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 97.1429 % (> 96.0714 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 95.5556 % (> 93.8889 %) |
| <b>Type C</b> | 100.0000 % (> 99.8815 %) | n/a (n/a)               |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20823     | 20823               | 0.00                         | 141.27                          |
| 21276     | 20823               | 14.37                        | 142.22                          |
| 21534     | 21534               | 0.00                         | 131.42                          |
| 21687     | 21534               | 9.10                         | 140.96                          |
| 21818     | 21818               | 0.00                         | 141.49                          |
| 23124     | 20823               | 24.82                        | 140.29                          |
| 23295     | 23295               | 0.00                         | 150.46                          |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Gramicidin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20203-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Gramicidin; Gramicidinum

### Special notes

When selecting the *Gramicidin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Gramicidin*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate        |
|----------|------------|------------------|-----------|---------|--------------------|
| Fagron   | Gramicidin | 13J15-N02        | 21253     | 40      | AR-15-FG-000813-01 |
| Fagron   | Gramicidin | 14C07-B06-292886 | 21544     | 40      | pending            |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Gramicidin*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *Gramicidin*.

| Supplier | Substance  | Batch            | Sample ID | Spectra |
|----------|------------|------------------|-----------|---------|
| Fagron   | Gramicidin | 11A27-N32        | 20203     | 40      |
| Fagron   | Gramicidin | 15H18-B01-316269 | 22748     | 40      |

- 146 649 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 12 spectra from 5 *Apo-Ident* customers from 10 batches from the substance/substance group *Gramicidin*.

| Supplier | Substance  | Batch            | Spectra |
|----------|------------|------------------|---------|
| Fagron   | Gramicidin | 12I07-N03        | 1       |
| Fagron   | Gramicidin | 11F-24-N03       | 1       |
| Fagron   | Gramicidin | 12K22-N12        | 1       |
| Caelo    | Gramicidin | 13J15-N02        | 1       |
| Fagron   | Gramicidin | 14H06-B03-297614 | 3       |
| Fagron   | Gramicidin | 15C11-B04-306766 | 1       |

*continued on the next page*

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| Supplier | Substance  | Batch     | Spectra |
|----------|------------|-----------|---------|
| Fagron   | Gramicidin | B3200202  | 1       |
| Fagron   | Gramicidin | B3200266  | 1       |
| Fagron   | Gramicidin | 12/07-N03 | 1       |
| Fagron   | Gramicidin | 12F18-N09 | 1       |

- 69 621 spectra from 414 *Apo-Ident* customers from a total of 23 791 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Gramicidin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Gramicidin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 73            | 7              | 146 649       |
| <b>Type C</b> | 0              | 12            | 0              | 69 621        |

The substance/substance group *Gramicidin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 91.2500 % (> 87.5000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21253     | 21253               | 0.00                         | 20.53                           |
| 21544     | 21544               | 0.00                         | 22.60                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Griseofulvin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20939-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Griseofulvin; Griseofulvinum

### Special notes

When selecting the *Griseofulvin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Griseofulvin*:

| Supplier | Substance    | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------|------------------|-----------|---------|-------------|
| Fagron   | Griseofulvin | 13D19-N03        | 20939     | 40      | 1401419     |
| Fagron   | Griseofulvin | 14E16-B01-296834 | 21725     | 40      | 20140526    |
| Fagron   | Griseofulvin | 16F13-B06-330832 | 23594     | 40      | 20160713    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Griseofulvin*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *Griseofulvin*.

| Supplier | Substance    | Batch            | Sample ID          | Spectra |
|----------|--------------|------------------|--------------------|---------|
| Fagron   | Griseofulvin | 9B13-N08         | 20236              | 40      |
| Fagron   | Griseofulvin | 14E16-B01-296834 | 21725 <sup>†</sup> | 20      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 35 spectra from 18 *Apo-Ident* customers from 25 batches from the substance/substance group *Griseofulvin*.

| Supplier | Substance    | Batch     | Spectra |
|----------|--------------|-----------|---------|
| Fagron   | Griseofulvin | 13L13-B08 | 1       |
| Fagron   | Griseofulvin | 130922    | 1       |
| Fagron   | Griseofulvin | 13L-13B08 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

continued from previous page

| Supplier     | Substance    | Batch            | Spectra |
|--------------|--------------|------------------|---------|
| Fagron       | Griseofulvin | 13L13-B08-290316 | 3       |
| Fagron       | Griseofulvin | 13L13-B08-290317 | 1       |
| Phönix Gotha | Griseofulvin | 140410           | 1       |
| Fagron       | Griseofulvin | 14E16-B01-300366 | 2       |
| Fagron       | Griseofulvin | 140410           | 2       |
| Fagron       | Griseofulvin | 14E16-B01-300367 | 1       |
| Fagron       | Griseofulvin | 15062015A        | 1       |
| Fagron       | Griseofulvin | 15B10-B06        | 1       |
| Fagron       | Griseofulvin | 15B10-B06-306547 | 1       |
| Fagron       | Griseofulvin | 15B10-B06-306663 | 1       |
| Fagron       | Griseofulvin | 15L03-B04-315624 | 3       |
| Fagron       | Griseofulvin | 15B10-B06-396547 | 1       |
| Fagron       | Griseofulvin | 16F13-B06-323067 | 1       |
| Caelo        | Griseofulvin | 16F13-B06-323068 | 1       |
| Fagron       | Griseofulvin | 16F13-B06-323068 | 2       |
| Fagron       | Griseofulvin | 16F13-B06-330832 | 1       |
| Fagron       | Griseofulvin | HH160510         | 1       |
| Caelo        | Griseofulvin | 100910           | 1       |
| Fagron       | Griseofulvin | 10F03-N12        | 1       |
| Fagron       | Griseofulvin | 11F30-N16        | 1       |
| Sanacorp/ F  | Griseofulvin | 12B06-N07        | 1       |
| Phönix Gotha | Griseofulvin | 12D04-N12        | 2       |
| Fagron       | Griseofulvin | 12F18-N04        | 1       |
| Fagron       | Griseofulvin | 13D19-N03        | 1       |

- 69 598 spectra from 414 *Apo-Ident* customers from a total of 23 776 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Griseofulvin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Griseofulvin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 32            | 3              | 69 598        |

The substance/substance group *Griseofulvin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 91.4286 % (> 82.8571 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several

new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20939     | 20939               | 0.00                         | 55.93                           |
| 21725     | 20939               | 9.13                         | 57.70                           |
| 23594     | 20939               | 3.93                         | 57.74                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Guaifenesin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20551-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Guaifenesin; Guaifenesinum; Guajacolum glycerinicum

### Special notes

When selecting the *Guaifenesin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Guaifenesin*:

| Supplier | Substance   | Batch      | Sample ID | Spectra | Certificate |
|----------|-------------|------------|-----------|---------|-------------|
| Euro OTC | Guaifenesin | 1212002-01 | 21287     | 40      | 20121214    |
| Euro OTC | Guaifenesin | 1506044    | 21864     | 40      | 20150708*   |
| Euro OTC | Guaifenesin | 1605005    | 22555     | 40      | 20160525*   |
| Caelo    | Guaifenesin | 163333     | 23051     | 40      | 20161221*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Guaifenesin*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 6 reference samples from the substance/substance group *Guaifenesin*.

| Supplier | Substance   | Batch    | Sample ID          | Spectra |
|----------|-------------|----------|--------------------|---------|
| Caelo    | Guaifenesin | 11277411 | 20551              | 40      |
| Caelo    | Guaifenesin | 11277411 | 20563              | 40      |
| Euro OTC | Guaifenesin | 1506044  | 21864 <sup>†</sup> | 20      |
| Euro OTC | Guaifenesin | 1701011  | 22993              | 40      |
| Euro OTC | Guaifenesin | 1706006  | 23551              | 40      |
| Caelo    | Guaifenesin | 172496   | 23644              | 40      |

- 146 509 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 7 spectra from 4 *Apo-Ident* customers from 6 batches from the substance/substance group *Guaifenesin*.

| Supplier           | Substance   | Batch            | Spectra |
|--------------------|-------------|------------------|---------|
| Phoenix 05.07.2014 | Guaifenesin | 1402023-01       | 2       |
| Euro OTC           | Guaifenesin | 1409006-02       | 1       |
| Caelo              | Guaifenesin | 14B20-B03-296249 | 1       |
| Caelo              | Guaifenesin | 1212002-01       | 1       |
| Caelo              | Guaifenesin | 12277311         | 1       |
| Caelo              | Guaifenesin | 12277307         | 1       |

- 69 626 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Guaifenesin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Guaifenesin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 220           | 0              | 146 509       |
| <b>Type C</b> | 0              | 6             | 1              | 69 626        |

The substance/substance group *Guaifenesin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.2727 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21287     | 22555               | 10.61                        | 35.35                           |
| 21864     | 21864               | 0.00                         | 35.25                           |
| 22555     | 22555               | 0.00                         | 34.56                           |
| 23051     | 23051               | 0.00                         | 35.13                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Hard fat (601)**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20496-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Hard fat (601); Adeps solidus (601)

### Special notes

When selecting the *Hard fat (601)* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hard fat (601)*:

| Supplier | Substance      | Batch    | Sample ID | Spectra | Certificate |
|----------|----------------|----------|-----------|---------|-------------|
| Caelo    | Hard fat (601) | 13296104 | 20997     | 40      | 1403144     |
| Caelo    | Hard fat (601) | 15184905 | 21974     | 40      | 20150611    |
| Caelo    | Hard fat (601) | 172178   | 23690     | 40      | 20170817*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Hard fat (601)*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Hard fat (601)*.

| Supplier | Substance      | Batch    | Sample ID          | Spectra |
|----------|----------------|----------|--------------------|---------|
| Caelo    | Hard fat (601) | 11320006 | 20496              | 40      |
| Caelo    | Hard fat (601) | 14099604 | 21488              | 40      |
| Caelo    | Hard fat (601) | 15184905 | 21974 <sup>†</sup> | 20      |
| Caelo    | Hard fat (601) | 162364   | 22648              | 40      |
| Caelo    | Hard fat (601) | 162364   | 22766              | 40      |

- 146 549 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 3 spectra from 1 *Apo-Ident* customers from 3 batches from the substance/substance group *Hard fat (601)*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance      | Batch    | Spectra |
|----------|----------------|----------|---------|
| Caelo    | Hard fat (601) | 15184901 | 1       |
| Caelo    | Hard fat (601) | 13296104 | 1       |
| Caelo    | Hard fat (601) | 14099608 | 1       |

- 69 630 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hard fat (601)* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hard fat (601)* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 135           | 45             | 146 549       |
| <b>Type C</b> | 0              | 2             | 1              | 69 630        |

The substance/substance group *Hard fat (601)* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 75.0000 % (> 73.3333 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8817 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20997     | 20997               | 0.00                         | 18.49                           |
| 21974     | 20997               | 8.14                         | 21.00                           |
| 23690     | 23690               | 0.00                         | 36.64                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Heparin sodium**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20638-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Heparin sodium; Heparinum natricum; Natrii heparini

### Special notes

When selecting the *Heparin sodium* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Heparin sodium*:

| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate        |
|----------|----------------|------------------|-----------|---------|--------------------|
| Fagron   | Heparin sodium | 12H30-N07        | 20798     | 40      | 1404230            |
| Euro OTC | Heparin sodium | 12050009-03      | 21294     | 40      | AR-15-FG-007427-02 |
| Euro OTC | Heparin sodium | 1605022-01       | 22804     | 40      | 9699               |
| Fagron   | Heparin sodium | 12L20-B01-317990 | 22824     | 40      | 20130312           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Heparin sodium*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 75 spectra of 2 reference samples from the substance/substance group *Heparin sodium*.

| Supplier | Substance      | Batch            | Sample ID | Spectra |
|----------|----------------|------------------|-----------|---------|
| Euro OTC | Heparin sodium | 1202002-01       | 20638     | 40      |
| Fagron   | Heparin sodium | 16I26-B02-332108 | 23591     | 35      |

- 146 654 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 17 spectra from 8 *Apo-Ident* customers from 12 batches from the substance/substance group *Heparin sodium*.

| Supplier | Substance      | Batch            | Spectra |
|----------|----------------|------------------|---------|
| Fagron   | Heparin sodium | 12G19-B02-313422 | 1       |
| Fagron   | Heparin sodium | 12I20-B01-323107 | 1       |
| Fagron   | Heparin sodium | 13G03-N13        | 3       |
| Fagron   | Heparin sodium | 14D09-B08        | 1       |

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| Supplier | Substance      | Batch            | Spectra |
|----------|----------------|------------------|---------|
| Fagron   | Heparin sodium | 14D09-B08-293944 | 2       |
| Fagron   | Heparin sodium | 14D09-B08-307077 | 1       |
| Fiebig   | Heparin sodium | 16190116C0       | 1       |
| Fagron   | Heparin sodium | 16I26-B02-327885 | 1       |
| Fagron   | Heparin sodium | 12H30-N07        | 2       |
| Fagron   | Heparin sodium | 16I26-B02-332108 | 1       |
| Fagron   | Heparin sodium | 11190188SH       | 2       |
| Euro OTC | Heparin sodium | 1202002-01       | 1       |

- 69 616 spectra from 414 *Apo-Ident* customers from a total of 23 789 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Heparin sodium* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Heparin sodium* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 73            | 2              | 146 654       |
| <b>Type C</b> | 0              | 14            | 3              | 69 616        |

The substance/substance group *Heparin sodium* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 97.3333 % (> 93.3333 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20798     | 20798               | 0.00                         | 55.19                           |
| 21294     | 21294               | 0.00                         | 71.39                           |
| 22804     | 22804               | 0.00                         | 61.64                           |
| 22824     | 20798               | 15.49                        | 65.42                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Histamine dihydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20963-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Histamine dihydrochloride; Histamini dihydrochloridum; Histaminum hydrochloricum

### Special notes

When selecting the *Histamine dihydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Histamine dihydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Histamine dihydr... | 1111004-02       | 20963     | 40      | 1403674     |
| Fagron   | Histamine dihydr... | 14G16-B02-299175 | 21668     | 80      | 20140729    |
| Euro OTC | Histamine dihydr... | 1506030          | 21863     | 40      | 20150706*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 3 reference samples from the substance/substance group *Histamine dihydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 160 spectra of 5 reference samples from the substance/substance group *Histamine dihydrochloride*.

| Supplier    | Substance                 | Batch            | Sample ID          | Spectra |
|-------------|---------------------------|------------------|--------------------|---------|
| zu erfassen | Histamine dihydrochloride | pending          | 20158              | 40      |
| Fagron      | Histamine dihydrochloride | 14G16-B02-299175 | 21668 <sup>†</sup> | 20      |
| Euro OTC    | Histamine dihydrochloride | 1506030          | 21863 <sup>†</sup> | 20      |
| Fagron      | Histamine dihydrochloride | 15C25-B50-331242 | 23196              | 40      |
| Fagron      | Histamine dihydrochloride | 15C25-B50-331242 | 23197              | 40      |

- 146 569 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 41 spectra from 20 *Apo-Ident* customers from 21 batches from the substance/substance group *Histamine dihydrochloride*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                   | Substance                 | Batch            | Spectra |
|----------------------------|---------------------------|------------------|---------|
| Euro OTC                   | Histamine dihydrochloride | 3031503          | 1       |
| Caelo                      | Histamine dihydrochloride | 130500601        | 1       |
| Euro OTC                   | Histamine dihydrochloride | 1506030-01       | 2       |
| Euro OTC                   | Histamine dihydrochloride | 1411012-01       | 1       |
| Fagron                     | Histamine dihydrochloride | 15C25-B50-331242 | 1       |
| Fagron                     | Histamine dihydrochloride | 15E08-B06-313037 | 2       |
| Euro OTC                   | Histamine dihydrochloride | 1104004-02       | 1       |
| Euro OTC                   | Histamine dihydrochloride | 1104004-03       | 1       |
| Fagron                     | Histamine dihydrochloride | 454545           | 1       |
| Euro OTC                   | Histamine dihydrochloride | 111004-02        | 1       |
| Euro OTC                   | Histamine dihydrochloride | 1111004-01       | 7       |
| Alliance Healthcare/Now... | Histamine dihydrochloride | 1111004-01       | 1       |
| Euro OTC                   | Histamine dihydrochloride | 1111004-02       | 3       |
| Fagron                     | Histamine dihydrochloride | 11E25-N07        | 2       |
| Fagron                     | Histamine dihydrochloride | 12D02-N16        | 1       |
| Caelo                      | Histamine dihydrochloride | 1111004-02       | 1       |
| Fagron                     | Histamine dihydrochloride | 12E29-N09        | 2       |
| Phönix                     | Histamine dihydrochloride | 12e29n09         | 1       |
| Fagron                     | Histamine dihydrochloride | 12K06-N08        | 7       |
| Euro OTC                   | Histamine dihydrochloride | 1305006-01       | 1       |
| Euro OTC                   | Histamine dihydrochloride | 20021412         | 1       |
| Fagron                     | Histamine dihydrochloride | 25051202         | 1       |
| Fagron                     | Histamine dihydrochloride | 28051305         | 1       |

- 69 592 spectra from 414 *Apo-Ident* customers from a total of 23 780 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Histamine dihydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Histamine dihydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 156           | 4              | 146 569       |
| <b>Type C</b> | 0              | 41            | 0              | 69 592        |

The substance/substance group *Histamine dihydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 97.5000 % (> 95.6250 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 85.3659 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20963     | 20963               | 0.00                         | 81.65                           |
| 21668     | 21863               | 5.10                         | 80.82                           |
| 21863     | 21863               | 0.00                         | 81.68                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Hyaluronic acid sodium salt**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21036-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Hyaluronic acid sodium salt; Natrii Hyaluronas

### Special notes

When selecting the *Hyaluronic acid sodium salt* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hyaluronic acid sodium salt*:

| Supplier | Substance           | Batch       | Sample ID | Spectra | Certificate |
|----------|---------------------|-------------|-----------|---------|-------------|
| Euro OTC | Hyaluronic acid ... | L1302028-01 | 21036     | 40      | 1403532     |
| Euro OTC | Hyaluronic acid ... | L1302028-01 | 21074     | 60      | 20130314    |
| Audor    | Hyaluronic acid ... | AP30101404H | 22262     | 35      | pending     |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 135 spectra of 3 reference samples from the substance/substance group *Hyaluronic acid sodium salt*. These samples are listed above in the [calibration samples](#) section.
- 71 251 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 170 spectra of 5 reference samples from the substance/substance group *Hyaluronic acid sodium salt*.

| Supplier     | Substance                   | Batch       | Sample ID          | Spectra |
|--------------|-----------------------------|-------------|--------------------|---------|
| Dr. Behr     | Hyaluronic acid sodium salt | 7071105     | 20518              | 40      |
| Spinnrad     | Hyaluronic acid sodium salt | 51240342    | 20779              | 40      |
| Audor Pharma | Hyaluronic acid sodium salt | AP30101404H | 22262 <sup>†</sup> | 20      |
| Audor Pharma | Hyaluronic acid sodium salt | AP30101702H | 23602              | 40      |
| Caelo        | Hyaluronic acid sodium salt | 172347      | 23620              | 30      |

- 146 559 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 20 spectra from 10 *Apo-Ident* customers from 14 batches from the substance/substance group *Hyaluronic acid sodium salt*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier     | Substance                   | Batch       | Spectra |
|--------------|-----------------------------|-------------|---------|
| Caelo        | Hyaluronic acid sodium salt | 14188702    | 1       |
| Calo/AHD     | Hyaluronic acid sodium salt | 14364704    | 1       |
| Audor Pharma | Hyaluronic acid sodium salt | AP30101305H | 2       |
| Audor Pharma | Hyaluronic acid sodium salt | AP30101404H | 2       |
| Fagron       | Hyaluronic acid sodium salt | L1311012-01 | 1       |
| Audor Pharma | Hyaluronic acid sodium salt | AP30101505H | 1       |
| Euro OTC     | Hyaluronic acid sodium salt | L1512025-01 | 2       |
| Caelo        | Hyaluronic acid sodium salt | 1263303     | 1       |
| Audor Pharma | Hyaluronic acid sodium salt | 30101204H   | 1       |
| Audor Pharma | Hyaluronic acid sodium salt | AP30101204H | 1       |
| Caelo        | Hyaluronic acid sodium salt | 14364706    | 2       |
| Caelo        | Hyaluronic acid sodium salt | 14364707    | 1       |
| Caelo        | Hyaluronic acid sodium salt | 15204901    | 1       |
| Caelo        | Hyaluronic acid sodium salt | 15204903    | 3       |

- 69 613 spectra from 414 *Apo-Ident* customers from a total of 23 787 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hyaluronic acid sodium salt* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hyaluronic acid sodium salt* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 135           | 0              | 71 251        |
| <b>Type B</b> | 0              | 127           | 43             | 146 546       |
| <b>Type C</b> | 0              | 17            | 3              | 69 613        |

The substance/substance group *Hyaluronic acid sodium salt* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.5556 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 74.7059 % (> 72.9412 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 85.0000 % (> 70.0000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21036     | 21036               | 0.00                         | 17.58                           |
| 21074     | 21036               | 2.16                         | 19.53                           |
| 22262     | 22262               | 0.00                         | 28.79                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Hydrochlorothiazide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20323-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Hydrochlorothiazide; Hydrochlorothiazidum

### Special notes

When selecting the *Hydrochlorothiazide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hydrochlorothiazide*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate        |
|----------|---------------------|-----------|-----------|---------|--------------------|
| Fagron   | Hydrochlorothiaz... | 11L01-N02 | 20888     | 40      | 20111209           |
| Caelo    | Hydrochlorothiaz... | 13008505  | 21589     | 40      | AR-15-FG-014461-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Hydrochlorothiazide*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Hydrochlorothiazide*.

| Supplier | Substance           | Batch            | Sample ID          | Spectra |
|----------|---------------------|------------------|--------------------|---------|
| Fagron   | Hydrochlorothiazide | 11E04-N10        | 20323              | 40      |
| Fagron   | Hydrochlorothiazide | 11L01-N02        | 20378              | 40      |
| Caelo    | Hydrochlorothiazide | 13008505         | 21589 <sup>†</sup> | 20      |
| Caelo    | Hydrochlorothiazide | 14009701         | 23116              | 40      |
| Fagron   | Hydrochlorothiazide | 16F17-B07-327489 | 23600              | 40      |

- 146 549 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 92 spectra from 61 *Apo-Ident* customers from 38 batches from the substance/substance group *Hydrochlorothiazide*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                   | Substance           | Batch             | Spectra |
|----------------------------|---------------------|-------------------|---------|
| Fagron                     | Hydrochlorothiazide | 12A03-B40         | 3       |
| Fagron                     | Hydrochlorothiazide | 12A03-B40-286111  | 3       |
| Fagron                     | Hydrochlorothiazide | 12A03-B40-286110  | 1       |
| Fagron                     | Hydrochlorothiazide | 12B23-N05         | 1       |
| Fagron                     | Hydrochlorothiazide | 12L14-N11         | 3       |
| Caelo                      | Hydrochlorothiazide | 13008507          | 1       |
| Caelo                      | Hydrochlorothiazide | 13008509          | 5       |
| Fagron                     | Hydrochlorothiazide | 13C25-N08         | 7       |
| Caelo                      | Hydrochlorothiazide | 14009701          | 15      |
| Fagron                     | Hydrochlorothiazide | 14B10B01          | 1       |
| Caelo                      | Hydrochlorothiazide | 14B10-B01-294558  | 2       |
| Fagron                     | Hydrochlorothiazide | 14B10-B01-294558  | 6       |
| Fagron                     | Hydrochlorothiazide | 14b10-b01-294558  | 1       |
| Fagron                     | Hydrochlorothiazide | 14B10-B01-300822  | 2       |
| Fagron                     | Hydrochlorothiazide | 14B10-B-01-300822 | 1       |
| Caelo                      | Hydrochlorothiazide | 14B10-B01-305043  | 1       |
| Caesar & Loretz GmbH Hi... | Hydrochlorothiazide | 152310            | 3       |
| Phoenix                    | Hydrochlorothiazide | 15231003          | 1       |
| Caelo                      | Hydrochlorothiazide | 15231003          | 3       |
| Caelo                      | Hydrochlorothiazide | 15231008          | 1       |
| Fagron                     | Hydrochlorothiazide | 15K16-B01         | 1       |
| Fagron                     | Hydrochlorothiazide | 15E04-B03-309670  | 1       |
| Fagron                     | Hydrochlorothiazide | 15K16-B01-319833  | 3       |
| Fagron                     | Hydrochlorothiazide | 16F17-B07-324062  | 4       |
| Fagron                     | Hydrochlorothiazide | 5013Q-03660       | 1       |
| Caelo                      | Hydrochlorothiazide | P157/14           | 1       |
| Caelo                      | Hydrochlorothiazide | 16F17B07327489    | 1       |
| Fagron                     | Hydrochlorothiazide | CQ1108            | 1       |
| Sanacorp                   | Hydrochlorothiazide | 12A03-B40-26111   | 1       |
| Caelo                      | Hydrochlorothiazide | 13008504          | 1       |
| Caelo                      | Hydrochlorothiazide | CQ1108            | 1       |
| Fagron                     | Hydrochlorothiazide | CR0601            | 1       |
| Fagron                     | Hydrochlorothiazide | 11E04-N10         | 1       |
| Fagron                     | Hydrochlorothiazide | 11G12-N12         | 1       |
| Fagron                     | Hydrochlorothiazide | 11101-n02         | 2       |
| Fagron                     | Hydrochlorothiazide | 11L01-N02         | 2       |
| Caelo                      | Hydrochlorothiazide | 11101n02          | 1       |
| Fagron                     | Hydrochlorothiazide | 11L01-No2         | 1       |
| Fagron                     | Hydrochlorothiazide | 11Lo1-No2         | 1       |
| Gehe                       | Hydrochlorothiazide | 12E04-N02         | 1       |
| Fagron                     | Hydrochlorothiazide | 12E04-N02         | 1       |
| Caelo                      | Hydrochlorothiazide | 12L14-N11         | 2       |
| Fagron                     | Hydrochlorothiazide | 2002311234        | 1       |

- 69 541 spectra from 414 *Apo-Ident* customers from a total of 23 763 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hydrochlorothiazide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hydrochlorothiazide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The

following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 80            | 0              | 71 306        |
| Type B | 0              | 169           | 11             | 146 549       |
| Type C | 0              | 78            | 14             | 69 541        |

The substance/substance group *Hydrochlorothiazide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 93.8889 % (> 92.2222 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 84.7826 % (> 81.5217 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20888     | 21589               | 13.01                        | 21.02                           |
| 21589     | 21589               | 0.00                         | 19.87                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Hydrocortisone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20006-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Hydrocortisone; Hydrocortisonum purum

### Special notes

When selecting the *Hydrocortisone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hydrocortisone*:

| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate |
|----------|----------------|------------------|-----------|---------|-------------|
| Euro OTC | Hydrocortisone | 1206018-01       | 21293     | 40      | 20130727    |
| Caelo    | Hydrocortisone | 13341502         | 21461     | 40      | 20131203    |
| Euro OTC | Hydrocortisone | 1509029          | 21899     | 40      | 20151014*   |
| Fagron   | Hydrocortisone | 16A19-B06-320970 | 22829     | 40      | 20160204    |
| Fagron   | Hydrocortisone | 16A19-B06-321981 | 22838     | 40      | 1702302     |

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| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate |
|----------|----------------|------------------|-----------|---------|-------------|
| Euro OTC | Hydrocortisone | 1611016          | 22910     | 40      | 20161220*   |
| Fagron   | Hydrocortisone | 16H01-B01-326071 | 22928     | 40      | 20160907    |
| Euro OTC | Hydrocortisone | 1509029          | 21899SI   | 36      | 20151014*   |
| Fagron   | Hydrocortisone | 16A19-B06-320970 | 22829SI   | 30      | 20160204    |
| Fagron   | Hydrocortisone | 16H01-B01-326071 | 22928SI   | 40      | 20160907    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 386 spectra of 10 reference samples from the substance/substance group *Hydrocortisone*. These samples are listed above in the [calibration samples](#) section.
- 71 000 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 594 spectra of 18 reference samples from the substance/substance group *Hydrocortisone*.

| Supplier | Substance      | Batch            | Sample ID            | Spectra |
|----------|----------------|------------------|----------------------|---------|
| Caelo    | Hydrocortisone | 91050209         | 20006                | 30      |
| Caelo    | Hydrocortisone | 10083801         | 20110                | 40      |
| Caelo    | Hydrocortisone | 13341502         | 21461 <sup>†</sup>   | 20      |
| Caelo    | Hydrocortisone | 13341502         | 21463                | 60      |
| Euro OTC | Hydrocortisone | 1509029          | 21899 <sup>†</sup>   | 20      |
| Caelo    | Hydrocortisone | 160952           | 22778                | 40      |
| Fagron   | Hydrocortisone | 16A19-B06-321981 | 22837                | 40      |
| Caelo    | Hydrocortisone | 171194           | 23340                | 20      |
| Caelo    | Hydrocortisone | 171194           | 23659                | 30      |
| Fagron   | Hydrocortisone | 16A19-B06-320970 | not required         | 20      |
| Caelo    | Hydrocortisone | 13341502         | 21463SI              | 60      |
| Euro OTC | Hydrocortisone | 1509029          | 21899SI <sup>†</sup> | 15      |
| Caelo    | Hydrocortisone | 160952           | 22778SI              | 40      |
| Fagron   | Hydrocortisone | 16A19-B06-321981 | 22837SI              | 30      |
| Fagron   | Hydrocortisone | 16A19-B06-321981 | 22838SI              | 31      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

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| Supplier | Substance      | Batch   | Sample ID | Spectra |
|----------|----------------|---------|-----------|---------|
| Euro OTC | Hydrocortisone | 1611016 | 22910SI   | 40      |
| Caelo    | Hydrocortisone | 171194  | 23340SI   | 28      |
| Caelo    | Hydrocortisone | 171194  | 23659SI   | 30      |

- 146 135 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 877 spectra from 263 *Apo-Ident* customers from 216 batches from the substance/substance group *Hydrocortisone*.

| Supplier                   | Substance      | Batch            | Spectra |
|----------------------------|----------------|------------------|---------|
| Caelo                      | Hydrocortisone | 13341504         | 6       |
| Euro OTC                   | Hydrocortisone | 1112030-01       | 12      |
| Caelo                      | Hydrocortisone | 12167007         | 9       |
| Caelo                      | Hydrocortisone | 12167010         | 12      |
| Caelo                      | Hydrocortisone | 13069501         | 8       |
| Caelo                      | Hydrocortisone | 13069510         | 6       |
| Caelo                      | Hydrocortisone | 14301312         | 6       |
| Großhandel                 | Hydrocortisone | 13H08-B01-285472 | 1       |
| Fagron                     | Hydrocortisone | 14I05-B02-300228 | 2       |
| Caelo                      | Hydrocortisone | 15278702         | 4       |
| Caelo                      | Hydrocortisone | 3081604          | 1       |
| Euro OTC                   | Hydrocortisone | 4091510          | 1       |
| Bestand                    | Hydrocortisone | 911Q-01719       | 2       |
| Caelo                      | Hydrocortisone | 9271205          | 2       |
| Euro OTC                   | Hydrocortisone | 6051502          | 1       |
| Euro OTC                   | Hydrocortisone | 715Q-01719       | 1       |
| Nachprüfung 2312           | Hydrocortisone | 10282201         | 1       |
| Caelo                      | Hydrocortisone | 10282208         | 2       |
| Euro OTC                   | Hydrocortisone | 1201618-01       | 1       |
| Euro OTC                   | Hydrocortisone | 120403701        | 3       |
| Euro OTC                   | Hydrocortisone | 1204037-01       | 25      |
| Euro OTC                   | Hydrocortisone | 1206018-01       | 26      |
| Caelo                      | Hydrocortisone | 1206018-01       | 1       |
| Fagron                     | Hydrocortisone | 120601801        | 1       |
| Gehe                       | Hydrocortisone | 1206018-01       | 2       |
| Fagron                     | Hydrocortisone | 12091401         | 1       |
| Caesar&Loretz GmbH         | Hydrocortisone | 12104308         | 1       |
| Caelo                      | Hydrocortisone | 13069505         | 4       |
| GEHE 14.04.2014            | Hydrocortisone | 13069509         | 1       |
| Alliance Health 11.01.2... | Hydrocortisone | 1315505          | 1       |
| Caelo                      | Hydrocortisone | 13155601         | 13      |
| AHD                        | Hydrocortisone | 13155601         | 2       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



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| <b>Supplier</b>           | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|---------------------------|------------------|------------------|----------------|
| Caelo                     | Hydrocortisone   | 13155602         | 9              |
| Caelo                     | Hydrocortisone   | 13155603         | 11             |
| Caelo                     | Hydrocortisone   | 13155604         | 10             |
| Caelo                     | Hydrocortisone   | 13155605         | 4              |
| Noweda                    | Hydrocortisone   | 13155605         | 1              |
| Caelo                     | Hydrocortisone   | 13155611         | 2              |
| GEHE 03.05.2014           | Hydrocortisone   | 13155605         | 1              |
| Caelo                     | Hydrocortisone   | 13155614         | 2              |
| Pharmacia&Upjohn/ Phönix  | Hydrocortisone   | 13155614         | 1              |
| Phönix Caesar u. Loretz   | Hydrocortisone   | 13225507         | 1              |
| Caelo                     | Hydrocortisone   | 13341501         | 9              |
| Caelo                     | Hydrocortisone   | 13341502         | 1              |
| Caelo                     | Hydrocortisone   | 13341502         | 9              |
| Phönix Gotha              | Hydrocortisone   | 13341502         | 1              |
| Alliance Health25.04.2014 | Hydrocortisone   | 13341503         | 3              |
| Caelo                     | Hydrocortisone   | 13341503         | 1              |
| Phönix                    | Hydrocortisone   | 13341504         | 2              |
| ahd,11,95EUR 10.04.14     | Hydrocortisone   | 13341504-07R07   | 1              |
| Caelo                     | Hydrocortisone   | 13341508         | 4              |
| Phönix                    | Hydrocortisone   | 13341508         | 1              |
| Caelo                     | Hydrocortisone   | 13341509         | 8              |
| Sanacorp                  | Hydrocortisone   | 13341509         | 1              |
| Caelo                     | Hydrocortisone   | 13341510         | 8              |
| Fagron                    | Hydrocortisone   | 13341510         | 1              |
| Caelo                     | Hydrocortisone   | 13341511         | 3              |
| Caelo                     | Hydrocortisone   | 13342504         | 1              |
| Caelo                     | Hydrocortisone   | 13H08-B01-285471 | 1              |
| Fagron                    | Hydrocortisone   | 13H08-B01-285472 | 4              |
| Fagron                    | Hydrocortisone   | 13H08-B01-285473 | 1              |
| Fagron                    | Hydrocortisone   | 13H08-B01-28571  | 1              |
| Fagron                    | Hydrocortisone   | 13K22-B01        | 2              |
| Fagron                    | Hydrocortisone   | 13K22-B011       | 1              |
| Fagron                    | Hydrocortisone   | 13K22-B01-288280 | 1              |
| Fagron                    | Hydrocortisone   | 13K22-B01-288282 | 1              |
| fargron                   | Hydrocortisone   | 13K22-B01-288284 | 1              |
| Fagron                    | Hydrocortisone   | 14/05-B02-300227 | 2              |
| Caelo                     | Hydrocortisone   | 140301305        | 1              |
| Fagron                    | Hydrocortisone   | 14/05-B02-300227 | 1              |
| Fagron                    | Hydrocortisone   |                  | 1              |
| EuRho                     | Hydrocortisone   | 1405001-01       | 3              |
| Euro OTC                  | Hydrocortisone   | 140500101        | 1              |
| Gehe                      | Hydrocortisone   | 1405001-01       | 2              |
| Euro OTC                  | Hydrocortisone   | 1405001-01       | 2              |
| Euro OTC                  | Hydrocortisone   | 1408023-01       | 4              |
| Phönix                    | Hydrocortisone   | 1408023-01       | 1              |
| Caelo                     | Hydrocortisone   | 14115103         | 4              |
| Caelo                     | Hydrocortisone   | 14115104         | 1              |
| Caelo                     | Hydrocortisone   | 14115105         | 3              |
| Berkel AHK                | Hydrocortisone   | 14115107         | 1              |
| Caelo                     | Hydrocortisone   | 14115107         | 9              |
| Caelo                     | Hydrocortisone   | 14115108         | 1              |
| Caelo                     | Hydrocortisone   | 14301304         | 5              |
| Caelo                     | Hydrocortisone   | 14301305         | 5              |
| Berkel AHK                | Hydrocortisone   | 14301305         | 1              |
| phönix                    | Hydrocortisone   | 14301306         | 1              |
| Caelo                     | Hydrocortisone   | 14301310         | 12             |
| Caelo                     | Hydrocortisone   | 14301306         | 1              |
| Caelo                     | Hydrocortisone   | 14301307         | 1              |
| AHD;19.06.15;18,70EUR     | Hydrocortisone   | 14301306         | 1              |
| Gehe,27.0415              | Hydrocortisone   | 14301310         | 1              |

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| <b>Supplier</b>           | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|---------------------------|------------------|------------------|----------------|
| Caelo                     | Hydrocortisone   | 14301311         | 8              |
| Caelo                     | Hydrocortisone   | 14301313         | 4              |
| Caelo                     | Hydrocortisone   | 1430312          | 1              |
| Caelo                     | Hydrocortisone   | 1431311          | 1              |
| Fagron                    | Hydrocortisone   | 14B04-B02        | 2              |
| Fagron                    | Hydrocortisone   | 14B04-B02-293422 | 1              |
| Fagron                    | Hydrocortisone   | 14B04-B02-293423 | 4              |
| Fagron                    | Hydrocortisone   | 14B04-B02-293424 | 3              |
| Bombastus                 | Hydrocortisone   | 14I05-B02-300227 | 1              |
| Fagron                    | Hydrocortisone   | 14I05-B02        | 2              |
| Fagron                    | Hydrocortisone   | 15/25-B01-318727 | 1              |
| Fagron                    | Hydrocortisone   | 15/25-B01-313084 | 1              |
| Euro OTC                  | Hydrocortisone   | 1501034-01       | 6              |
| Caelo                     | Hydrocortisone   | 1501034-01       | 1              |
| Caelo                     | Hydrocortisone   | 15021104         | 7              |
| Caelo                     | Hydrocortisone   | 1501105          | 1              |
| Caelo                     | Hydrocortisone   | 15021105         | 4              |
| Caelo                     | Hydrocortisone   | 15021106         | 2              |
| Caelo                     | Hydrocortisone   | 15021107         | 8              |
| Phönix Gotha              | Hydrocortisone   | 15021107         | 1              |
| Caesar & Loretz GmbH      | Hydrocortisone   | 15021107         | 1              |
| Euro OTC                  | Hydrocortisone   | 1505010601       | 1              |
| Caelo                     | Hydrocortisone   | 1505016-01       | 1              |
| Euro OTC                  | Hydrocortisone   | 1505016-01       | 22             |
| Euro OTC                  | Hydrocortisone   | 150516-01        | 1              |
| Euro OTC                  | Hydrocortisone   | 1509029-01       | 9              |
| Phoenix                   | Hydrocortisone   | 1509029-01       | 1              |
| Upjohn/Phönix             | Hydrocortisone   | 1509029-01       | 1              |
| Fagron                    | Hydrocortisone   | 1509029-01       | 1              |
| Caelo                     | Hydrocortisone   | 1509029-01       | 1              |
| Caelo                     | Hydrocortisone   | 150902901        | 1              |
| Euro OTC                  | Hydrocortisone   | 150929-01        | 1              |
| Sanacorp                  | Hydrocortisone   | 1509029-01       | 1              |
| Caelo                     | Hydrocortisone   | 1518013          | 1              |
| Caelo                     | Hydrocortisone   | 15181003         | 10             |
| Caesar&loretz,Phoenix     | Hydrocortisone   | 15181004         | 1              |
| Phönix Gotha              | Hydrocortisone   | 15181004         | 1              |
| Caelo                     | Hydrocortisone   | 15181004         | 8              |
| Beiersdorf/ Vedono        | Hydrocortisone   | 15181004         | 1              |
| Laborchemie Apolda/Phönix | Hydrocortisone   | 15181004         | 1              |
| Caelo                     | Hydrocortisone   | 15181006         | 15             |
| Caelo                     | Hydrocortisone   | 15181007         | 4              |
| Caelo                     | Hydrocortisone   | 15181008         | 1              |
| Caelo                     | Hydrocortisone   | 15181012         | 9              |
| Caesar & Loretz GmbH      | Hydrocortisone   | 15181012         | 1              |
| Caelo                     | Hydrocortisone   | 15181013         | 7              |
| sanacorp                  | Hydrocortisone   | 15181013         | 1              |
| Caelo                     | Hydrocortisone   | 15181014         | 2              |
| Caelo                     | Hydrocortisone   | 15216101         | 5              |
| Caelo                     | Hydrocortisone   | 15278703         | 9              |
| Caelo                     | Hydrocortisone   | 15278705         | 8              |
| Caelo                     | Hydrocortisone   | 15278706         | 1              |
| Caelo                     | Hydrocortisone   | 15356902         | 1              |
| Fagron                    | Hydrocortisone   | 15D14-B02        | 1              |
| Fagron                    | Hydrocortisone   | 15D14-B02-311696 | 4              |
| Fagron                    | Hydrocortisone   | 15I04-B03-315021 | 1              |
| Fagron                    | Hydrocortisone   | 15I25-B01-320154 | 1              |
| Fagron                    | Hydrocortisone   | 15I25-B01-318486 | 1              |
| Sanacorp                  | Hydrocortisone   | 16004603         | 1              |
| Caelo                     | Hydrocortisone   | 16004603         | 3              |

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| Supplier                    | Substance      | Batch            | Spectra |
|-----------------------------|----------------|------------------|---------|
| Caelo                       | Hydrocortisone | 16004604         | 14      |
| Bionorica                   | Hydrocortisone | 16004604         | 1       |
| Caelo                       | Hydrocortisone | 16004605         | 5       |
| Caelo                       | Hydrocortisone | 16004607         | 9       |
| Sanacorp                    | Hydrocortisone | 16004607         | 1       |
| Caelo                       | Hydrocortisone | 16004608         | 2       |
| Caelo                       | Hydrocortisone | 16004611         | 2       |
| Caelo                       | Hydrocortisone | 16004612         | 5       |
| Caelo                       | Hydrocortisone | 16095201         | 9       |
| Caelo                       | Hydrocortisone | 16095202         | 1       |
| / AHD                       | Hydrocortisone | 16095202         | 1       |
| Caelo                       | Hydrocortisone | 16095207         | 2       |
| Caelo                       | Hydrocortisone | 16095209         | 4       |
| Caelo                       | Hydrocortisone | 16095210         | 7       |
| Caelo                       | Hydrocortisone | 16095212         | 2       |
| Caelo                       | Hydrocortisone | 16095213         | 3       |
| Caelo                       | Hydrocortisone | 1611016-01       | 1       |
| Sanacorp                    | Hydrocortisone | 16255603         | 1       |
| Caelo                       | Hydrocortisone | 16272304         | 2       |
| Caelo                       | Hydrocortisone | 16255608         | 1       |
| Caelo                       | Hydrocortisone | 16272305         | 5       |
| Caesar&Loretz GmbH, Anza... | Hydrocortisone | 16272305         | 1       |
| Caelo                       | Hydrocortisone | 16272311         | 2       |
| Gehe                        | Hydrocortisone | 16272306         | 1       |
| Fagron                      | Hydrocortisone | 16H01-B01-324944 | 2       |
| Fagron                      | Hydrocortisone | 2180             | 1       |
| Caelo                       | Hydrocortisone | 260416v4         | 1       |
| Fagron                      | Hydrocortisone | 19051403         | 1       |
| Euro OTC                    | Hydrocortisone | 29011504         | 1       |
| Caelo                       | Hydrocortisone | 31032014D        | 1       |
| Caelo                       | Hydrocortisone | 42/AKD7          | 1       |
| Sanacorp                    | Hydrocortisone | 42/AKD6          | 1       |
| Sanacorp                    | Hydrocortisone |                  | 1       |
| Fagron                      | Hydrocortisone | K05B20130407M    | 1       |
| Fagron                      | Hydrocortisone | K05B20131101     | 1       |
| Caelo                       | Hydrocortisone | 113I-01719       | 1       |
| Caelo                       | Hydrocortisone | 810911           | 1       |
| Fagron                      | Hydrocortisone | 5061304          | 1       |
| Caelo                       | Hydrocortisone | 7101301          | 1       |
| Fagron                      | Hydrocortisone | 5061305          | 1       |
| Caelo                       | Hydrocortisone | 9360908          | 1       |
| Caelo                       | Hydrocortisone | 10340502         | 2       |
| Fagron                      | Hydrocortisone | 11/19-N03        | 2       |
| Caelo                       | Hydrocortisone | 11021302         | 1       |
| Fagron                      | Hydrocortisone | 11021403         | 1       |
| Euro OTC                    | Hydrocortisone | 1107005-01       | 2       |
| Euro OTC                    | Hydrocortisone | 1107005-02       | 7       |
| EuRho                       | Hydrocortisone | 1107005-02       | 1       |
| Euro OTC                    | Hydrocortisone | 1107005-03       | 10      |
| Anzag ek:10.01EUR 18.07.12  | Hydrocortisone | 1107005-03       | 1       |
| Caelo                       | Hydrocortisone | 11098413         | 1       |
| Caelo                       | Hydrocortisone | 1109845          | 1       |
| Sanacorp                    | Hydrocortisone | 1112030-01       | 1       |
| AHC 02.09.13 EK9,85         | Hydrocortisone | 1112030-01       | 1       |
| Caelo                       | Hydrocortisone | 11260302         | 1       |
| Caelo                       | Hydrocortisone | 11260303         | 1       |
| Gehe                        | Hydrocortisone | 11260303         | 1       |
| Caelo                       | Hydrocortisone | 11260304         | 1       |
| Gehe                        | Hydrocortisone | 11260305         | 1       |
| Caelo                       | Hydrocortisone | 11260305         | 1       |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|----------------------------|------------------|--------------|----------------|
| Anzag                      | Hydrocortisone   | 11260305     | 1              |
| Caelo                      | Hydrocortisone   | 11260307     | 2              |
| Caelo                      | Hydrocortisone   | 11260308     | 4              |
| Kehr                       | Hydrocortisone   | 11260309     | 1              |
| Sanacorp                   | Hydrocortisone   | 11260309     | 2              |
| Caelo                      | Hydrocortisone   | 11260309     | 3              |
| Phoenix am 11.06.2012      | Hydrocortisone   | 11260310     | 1              |
| Caelo                      | Hydrocortisone   | 11273703     | 1              |
| Caelo                      | Hydrocortisone   | 11273704     | 2              |
| Fagron                     | Hydrocortisone   | 11D07-N02    | 1              |
| Fagron                     | Hydrocortisone   | 11k18n01     | 1              |
| Fagron                     | Hydrocortisone   | 11K18-N01    | 2              |
| Fagron                     | Hydrocortisone   | 11L09-N06    | 1              |
| Caelo                      | Hydrocortisone   | 11L09-N06    | 1              |
| Großhandel                 | Hydrocortisone   | 11L09-N06    | 1              |
| Fagron                     | Hydrocortisone   | 11L09-N09    | 1              |
| Anzag 14.12.12 ek:10,01    | Hydrocortisone   | 1202032-01   | 1              |
| Phönix                     | Hydrocortisone   | 11119-N03    | 1              |
| Euro OTC                   | Hydrocortisone   | 1202032-01   | 3              |
| Gehe                       | Hydrocortisone   | 1202032-01   | 1              |
| A.H. 10.06.13 ek: 10,01EUR | Hydrocortisone   | 1204037-01   | 1              |
| Caelo                      | Hydrocortisone   | 120403701    | 1              |
| Phönix                     | Hydrocortisone   | 1204037-01   | 1              |
| Anzag/EuRho                | Hydrocortisone   | 1204037-01   | 1              |
| Euro OTC                   | Hydrocortisone   | 1204307-01   | 1              |
| Caelo                      | Hydrocortisone   | 12104301     | 2              |
| Caelo                      | Hydrocortisone   | 12104303     | 8              |
| Noweda                     | Hydrocortisone   | 12104303     | 1              |
| Caelo                      | Hydrocortisone   | 12104304     | 11             |
| Großhandel                 | Hydrocortisone   | 12104304     | 1              |
| Gehe                       | Hydrocortisone   | 12104304     | 3              |
| Caelo                      | Hydrocortisone   | 12104306     | 11             |
| Caelo                      | Hydrocortisone   | 12104305     | 3              |
| Caelo                      | Hydrocortisone   | 12104307     | 16             |
| Anzag 09.01.2013           | Hydrocortisone   | 12104307     | 1              |
| Caelo                      | Hydrocortisone   | 12104308     | 7              |
| Phönix Gotha               | Hydrocortisone   | 12104309     | 1              |
| Caelo                      | Hydrocortisone   | 12104309     | 2              |
| AHD, 02,12,13              | Hydrocortisone   | 12104309     | 1              |
| Caelo                      | Hydrocortisone   | 12119303     | 11             |
| Gehe                       | Hydrocortisone   | 12119303     | 1              |
| Fagron                     | Hydrocortisone   | 12119303     | 1              |
| Caelo                      | Hydrocortisone   | 12119304     | 3              |
| Kehr                       | Hydrocortisone   | 12167001     | 1              |
| Caelo                      | Hydrocortisone   | 12167001     | 8              |
| Noweda                     | Hydrocortisone   | 12167001     | 1              |
| Phönix                     | Hydrocortisone   | 12167001     | 3              |
| Klenk                      | Hydrocortisone   | 12167007     | 1              |
| Phönix                     | Hydrocortisone   | 12167010     | 1              |
| Caesar & Loretz GmbH       | Hydrocortisone   | 12167010     | 1              |
| Caelo                      | Hydrocortisone   | 1216707      | 1              |
| Kehr                       | Hydrocortisone   | 1219304      | 1              |
| Noweda                     | Hydrocortisone   | 12G19-N01    | 1              |
| Fagron                     | Hydrocortisone   | 12G19-N01    | 5              |
| Fagron                     | Hydrocortisone   | 12I25-N01    | 3              |
| Caelo                      | Hydrocortisone   | 12k08-n01    | 1              |
| Caelo                      | Hydrocortisone   | 13063501     | 1              |
| Caelo                      | Hydrocortisone   | 1306906      | 1              |
| Caelo                      | Hydrocortisone   | 13069502     | 9              |
| Caelo                      | Hydrocortisone   | 13069506     | 10             |

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| Supplier              | Substance      | Batch               | Spectra |
|-----------------------|----------------|---------------------|---------|
| Caesar & Loretz GmbH  | Hydrocortisone | 13069506            | 1       |
| AHD                   | Hydrocortisone | 13069507            | 1       |
| Caelo                 | Hydrocortisone | 13069507            | 5       |
| sana corp             | Hydrocortisone | 13069507            | 1       |
| Sanacorp              | Hydrocortisone | 13069509            | 1       |
| Caelo                 | Hydrocortisone | 13069509            | 2       |
| Gehe                  | Hydrocortisone | 13069510            | 1       |
| Phoenix               | Hydrocortisone | 13341504            | 1       |
| Fagron                | Hydrocortisone | 13341504            | 1       |
| Gehe                  | Hydrocortisone | 13H08-B01-285469    | 1       |
| Gehe                  | Hydrocortisone | 13H08-B01-285471    | 1       |
| Fagron                | Hydrocortisone | 13K22-B01-288284    | 1       |
| Fagron                | Hydrocortisone | 13H08B01285473      | 1       |
| Caelo                 | Hydrocortisone | 14B04-B02-293423    | 1       |
| Caesar&loretz,Phoenix | Hydrocortisone | 15021105            | 1       |
| Fagron                | Hydrocortisone | 15125-B01-318727    | 1       |
| Caelo                 | Hydrocortisone | 17081301            | 1       |
| Caelo                 | Hydrocortisone | 2013U-01719         | 1       |
| Caelo                 | Hydrocortisone | 21101303            | 1       |
| Caelo                 | Hydrocortisone | 24131-01719         | 1       |
| Caelo                 | Hydrocortisone | 2402211719          | 1       |
| Caelo                 | Hydrocortisone | 39/AKD17            | 1       |
| Caelo                 | Hydrocortisone | 3912Q-01719         | 1       |
| phönix                | Hydrocortisone |                     | 2       |
| Euro OTC              | Hydrocortisone | 4112A-01719         | 1       |
| Euro OTC              | Hydrocortisone | pzn4914731          | 1       |
| Caelo                 | Hydrocortisone | 9271202             | 1       |
| Anzag                 | Hydrocortisone | 1107005-02          | 1       |
| Fagron                | Hydrocortisone | 12/25-N01           | 1       |
| Fagron                | Hydrocortisone | 1204037-01          | 1       |
| Anzag                 | Hydrocortisone | 12104307            | 1       |
| Caelo                 | Hydrocortisone | 12167010-3437311151 | 1       |

- 68 756 spectra from 413 *Apo-Ident* customers from a total of 23 591 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hydrocortisone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hydrocortisone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 386           | 0              | 71 000        |
| Type B | 0              | 589           | 5              | 146 135       |
| Type C | 0              | 808           | 69             | 68 756        |

The substance/substance group *Hydrocortisone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.4456 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.1582 % (> 98.6532 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 92.1323 % (> 91.7902 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21293            | 22910                      | 4.79                                | 53.48                                  |
| 21461            | 21899                      | 1.98                                | 51.94                                  |
| 21899            | 21899                      | 0.00                                | 53.93                                  |
| 22829            | 22838                      | 6.58                                | 58.50                                  |
| 22838            | 22838                      | 0.00                                | 58.05                                  |
| 22910            | 22910                      | 0.00                                | 53.78                                  |
| 22928            | 22910                      | 1.98                                | 54.25                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Hydrocortisone acetate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20010-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Hydrocortisone acetate; Hydrocortisoni acetas; Hydrocortisonum aceticum

### Special notes

When selecting the *Hydrocortisone acetate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hydrocortisone acetate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Hydrocortisone a... | 1209003-01       | 21295     | 40      | 20121108    |
| Euro OTC | Hydrocortisone a... | 1508029          | 21889     | 40      | 20150902*   |
| Fagron   | Hydrocortisone a... | 15A30-B09-307090 | 22241     | 40      | 20150226    |
| Euro OTC | Hydrocortisone a... | 1604052          | 22564     | 40      | 20160525*   |
| Euro OTC | Hydrocortisone a... | 1209003-01       | 21295SI   | 30      | 20121108    |
| Euro OTC | Hydrocortisone a... | 1508029          | 21889SI   | 29      | 20150902*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 219 spectra of 6 reference samples from the substance/substance group *Hydrocortisone acetate*. These samples are listed above in the [calibration samples](#) section.
- 71 167 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 445 spectra of 15 reference samples from the substance/substance group *Hydrocortisone acetate*.

| Supplier | Substance              | Batch            | Sample ID            | Spectra |
|----------|------------------------|------------------|----------------------|---------|
| Caelo    | Hydrocortisone acetate | 82833159         | 20010                | 30      |
| Caelo    | Hydrocortisone acetate | 11263917         | 20602                | 40      |
| Caelo    | Hydrocortisone acetate | 13291708         | 21462                | 60      |
| Euro OTC | Hydrocortisone acetate | 1508029          | 21889 <sup>†</sup>   | 20      |
| Fagron   | Hydrocortisone acetate | 15A30-B09-307090 | 22241 <sup>†</sup>   | 20      |
| Caelo    | Hydrocortisone acetate | 16238706         | 23115                | 40      |
| Caelo    | Hydrocortisone acetate | 170862           | 23328                | 40      |
| Euro OTC | Hydrocortisone acetate | 1706021          | 23559                | 40      |
| Euro OTC | Hydrocortisone acetate | 1209003-01       | 21295SI <sup>†</sup> | 15      |
| Euro OTC | Hydrocortisone acetate | 1508029          | 21889SI <sup>†</sup> | 15      |
| Fagron   | Hydrocortisone acetate | 15A30-B09-307090 | 22241SI              | 24      |
| Euro OTC | Hydrocortisone acetate | 1604052          | 22564SI              | 30      |
| Caelo    | Hydrocortisone acetate | 16238706         | 23115SI              | 20      |
| Caelo    | Hydrocortisone acetate | 170862           | 23328SI              | 21      |
| Euro OTC | Hydrocortisone acetate | 1706021          | 23559SI              | 30      |

- 146 284 spectra from a total of 3184 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1189 spectra from 296 *Apo-Ident* customers from 235 batches from the substance/substance group *Hydrocortisone acetate*.

| Supplier                   | Substance              | Batch            | Spectra |
|----------------------------|------------------------|------------------|---------|
| Caelo                      | Hydrocortisone acetate | 2061401          | 1       |
| Caelo                      | Hydrocortisone acetate | 3110516          | 1       |
| Euro OTC                   | Hydrocortisone acetate | 508029-01        | 2       |
| Fagron                     | Hydrocortisone acetate | 11I01-N05        | 2       |
| Hedinger/Gehe              | Hydrocortisone acetate | 1112031-02       | 1       |
| Phönix                     | Hydrocortisone acetate | 1112031-02       | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1112031-02       | 5       |
| Caelo                      | Hydrocortisone acetate | 12021502         | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1205034-01       | 24      |
| Caelo                      | Hydrocortisone acetate | 1205034-01       | 4       |
| Euro OTC                   | Hydrocortisone acetate | 12090003-01      | 3       |
| Euro OTC                   | Hydrocortisone acetate | 1209003-01       | 20      |
| Großhandel                 | Hydrocortisone acetate | 1209003-01       | 1       |
| Caelo                      | Hydrocortisone acetate | 1209003-01       | 6       |
| Pharmacia&Upjohn Comp. ... | Hydrocortisone acetate | 1209003-01       | 1       |
| Euro OTC                   | Hydrocortisone acetate | 120900301        | 2       |
| Phoenix                    | Hydrocortisone acetate | 1209003-01       | 2       |
| EuRho/Phoenix              | Hydrocortisone acetate | 1209003-01       | 1       |
| Phoenix Goettin            | Hydrocortisone acetate | 1209003-01       | 1       |
| Caelo                      | Hydrocortisone acetate | 12182405         | 17      |
| Phönix                     | Hydrocortisone acetate | 12182405         | 1       |
| Fagron                     | Hydrocortisone acetate | 12330108         | 2       |
| Caelo                      | Hydrocortisone acetate | 12330102         | 8       |
| Caelo                      | Hydrocortisone acetate | 12330108         | 17      |
| Caelo                      | Hydrocortisone acetate | 12330111         | 8       |
| Caelo                      | Hydrocortisone acetate | 12330116         | 12      |
| Caelo                      | Hydrocortisone acetate | 12330112         | 15      |
| Fagron                     | Hydrocortisone acetate | 12K15-N04        | 7       |
| Fagron                     | Hydrocortisone acetate | 13/31-B07-290061 | 1       |
| Fagron                     | Hydrocortisone acetate | 13/31-B07-290062 | 1       |
| Caelo                      | Hydrocortisone acetate | 1315503          | 1       |
| Caesar&Loretz GmbH/Anzag   | Hydrocortisone acetate | 13155303         | 1       |
| Caelo                      | Hydrocortisone acetate | 13155303         | 7       |
| Caelo                      | Hydrocortisone acetate | 13155306         | 7       |
| Caelo                      | Hydrocortisone acetate | 13155307         | 3       |
| Caelo                      | Hydrocortisone acetate | 13155308         | 9       |
| Gehe                       | Hydrocortisone acetate | 13155308         | 1       |
| Caelo                      | Hydrocortisone acetate | 13291701         | 2       |
| Caelo                      | Hydrocortisone acetate | 13291704         | 3       |
| Caelo                      | Hydrocortisone acetate | 13291705         | 2       |
| Caelo                      | Hydrocortisone acetate | 13291706         | 11      |
| Sanacorp                   | Hydrocortisone acetate | 13291704         | 1       |
| Caelo                      | Hydrocortisone acetate | 13291707         | 14      |
| Herbasinica                | Hydrocortisone acetate | 13291707         | 1       |
| AHD                        | Hydrocortisone acetate | 13291707         | 1       |
| Cealo / Noweda             | Hydrocortisone acetate | 13291707         | 1       |
| Caelo                      | Hydrocortisone acetate | 13291708         | 8       |

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| Supplier                   | Substance              | Batch            | Spectra |
|----------------------------|------------------------|------------------|---------|
| Gehe                       | Hydrocortisone acetate | 13291708         | 1       |
| Caelo                      | Hydrocortisone acetate | 13291709         | 4       |
| AHDE 9.09.2014             | Hydrocortisone acetate | 13291711         | 1       |
| Caelo                      | Hydrocortisone acetate | 13291711         | 8       |
| Caelo                      | Hydrocortisone acetate | 13291714         | 1       |
| Fagron                     | Hydrocortisone acetate | 13F25-B05-300290 | 2       |
| Noweda                     | Hydrocortisone acetate | 13G09-N08        | 1       |
| Caelo                      | Hydrocortisone acetate | 1391704          | 1       |
| Caelo                      | Hydrocortisone acetate | 13G09-N08        | 1       |
| gehe                       | Hydrocortisone acetate | 13G09-N08        | 1       |
| Fagron                     | Hydrocortisone acetate | 13G09-N08        | 4       |
| Fagron                     | Hydrocortisone acetate | 13J31-B07        | 3       |
| Fagron                     | Hydrocortisone acetate | 13J31B07290061   | 1       |
| Fagron                     | Hydrocortisone acetate | 13J31-B07-290061 | 2       |
| Fagron                     | Hydrocortisone acetate | 13J31-B07-290062 | 2       |
| Euro OTC                   | Hydrocortisone acetate | 1404014-02       | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1404017-01       | 14      |
| Euro/Gehe                  | Hydrocortisone acetate | 1404017-01       | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1404017-02       | 5       |
| Euro OTC                   | Hydrocortisone acetate | 140401702        | 1       |
| Caelo                      | Hydrocortisone acetate | 14043901         | 13      |
| Apomix/Noweda              | Hydrocortisone acetate | 1404017-02       | 1       |
| Caelo                      | Hydrocortisone acetate | 14043902         | 10      |
| Phoenix 14.01.2015 EK: ... | Hydrocortisone acetate | 14043902         | 1       |
| Bombastus                  | Hydrocortisone acetate | 14043902         | 1       |
|                            | Hydrocortisone acetate | 14043902         | 1       |
| Caelo                      | Hydrocortisone acetate | 14043903         | 13      |
| GEHE 03.07.2014            | Hydrocortisone acetate | 14043903         | 1       |
| Caelo                      | Hydrocortisone acetate | 14043904         | 14      |
| Caelo                      | Hydrocortisone acetate | 14043905         | 9       |
| Gehe                       | Hydrocortisone acetate | 14043905         | 1       |
| Caelo                      | Hydrocortisone acetate | 14043906         | 10      |
| Fagron                     | Hydrocortisone acetate | 14043906         | 1       |
| Gehe                       | Hydrocortisone acetate | 14043906         | 3       |
| Caelo                      | Hydrocortisone acetate | 14043907         | 13      |
| Gehe                       | Hydrocortisone acetate | 14043907         | 1       |
| Caelo                      | Hydrocortisone acetate | 14043908         | 2       |
| Euro OTC                   | Hydrocortisone acetate | 1409005-01       | 14      |
| Euro/ Sanacorp             | Hydrocortisone acetate | 1409005-01       | 1       |
| Phönix/Lihua               | Hydrocortisone acetate | 1409005-01       | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1409005-02       | 5       |
| Caelo                      | Hydrocortisone acetate | 14144802         | 1       |
| Caelo                      | Hydrocortisone acetate | 14144803         | 10      |
| Phönix                     | Hydrocortisone acetate | 14144804         | 1       |
| Caelo                      | Hydrocortisone acetate | 14144804         | 5       |
| Fagron                     | Hydrocortisone acetate | 14144804         | 1       |
| Caelo                      | Hydrocortisone acetate | 14144805         | 14      |
| AHD;05,02,15; 12.48EUR     | Hydrocortisone acetate | 14144805         | 1       |
| Caelo                      | Hydrocortisone acetate | 14144806         | 13      |
| Caelo                      | Hydrocortisone acetate | 14144807         | 7       |
| Caelo                      | Hydrocortisone acetate | 1430102          | 1       |
| Caelo                      | Hydrocortisone acetate | 14301401         | 14      |
| Caelo                      | Hydrocortisone acetate | 14301402         | 7       |
| Caelo                      | Hydrocortisone acetate | 14301403         | 4       |
| Noweda 17.07.2015          | Hydrocortisone acetate | 14301403         | 1       |
| Caelo                      | Hydrocortisone acetate | 14301404         | 4       |
| Caelo                      | Hydrocortisone acetate | 14301405         | 15      |
| Caesar&Loretz GmbH/Anzag   | Hydrocortisone acetate | 14301405         | 2       |
| Caelo                      | Hydrocortisone acetate | 14301406         | 11      |
| Caelo                      | Hydrocortisone acetate | 14301407         | 14      |

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| Supplier                   | Substance              | Batch            | Spectra |
|----------------------------|------------------------|------------------|---------|
| Caelo                      | Hydrocortisone acetate | 14301408         | 8       |
| Fagron                     | Hydrocortisone acetate | 14A13-B04        | 1       |
| Fagron                     | Hydrocortisone acetate | 14A13-B04-294158 | 2       |
| Fagron                     | Hydrocortisone acetate | 14I16-B01-300292 | 2       |
| Euro OTC                   | Hydrocortisone acetate | 1501035-01       | 9       |
| Caelo                      | Hydrocortisone acetate | 1501035          | 1       |
| Euro OTC                   | Hydrocortisone acetate | 150103501        | 2       |
| Euro OTC                   | Hydrocortisone acetate | 1502000801       | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1505008          | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1505008-01       | 37      |
| Phoenix                    | Hydrocortisone acetate | 1505008-01       | 1       |
| Caelo                      | Hydrocortisone acetate | 1505008-01       | 3       |
| Euro OTC                   | Hydrocortisone acetate | 150500801        | 2       |
| Caesar & Loretz GmbH Hi... | Hydrocortisone acetate | 1505008-01       | 1       |
| Caelo                      | Hydrocortisone acetate | 15067003         | 8       |
| Caelo/Anzag                | Hydrocortisone acetate | 15067003         | 1       |
| caesar&lorenz,PHönix,1...  | Hydrocortisone acetate | 15067003         | 1       |
| Caesar u Loretz            | Hydrocortisone acetate | 15067003         | 1       |
| Caelo                      | Hydrocortisone acetate | 15067004         | 13      |
| Caesar & Loretz GmbH       | Hydrocortisone acetate | 15067004         | 1       |
| Caelo                      | Hydrocortisone acetate | 15067005         | 12      |
| Caelo                      | Hydrocortisone acetate | 15067006         | 5       |
| Caelo                      | Hydrocortisone acetate | 15067010         | 2       |
| Caelo                      | Hydrocortisone acetate | 15067011         | 6       |
| Caelo                      | Hydrocortisone acetate | 15067013         | 4       |
| Caelo                      | Hydrocortisone acetate | 15067017         | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1508029-01       | 21      |
| Europh-Gehe                | Hydrocortisone acetate | 1508029-01       | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1508029          | 1       |
| Euro/Alliance Healthcare   | Hydrocortisone acetate | 1508029-01       | 1       |
| Euro OTC                   | Hydrocortisone acetate | 150802901        | 1       |
| Caelo                      | Hydrocortisone acetate | 15216204         | 2       |
| Caelo                      | Hydrocortisone acetate | 15356901         | 9       |
| Caelo                      | Hydrocortisone acetate | 15356902         | 19      |
| Caelo                      | Hydrocortisone acetate | 15356903         | 11      |
| Caesar&Loretz GmbH/AHD     | Hydrocortisone acetate | 15356903         | 1       |
| Bombastus                  | Hydrocortisone acetate | 15356903         | 1       |
| Caelo                      | Hydrocortisone acetate | 15356904         | 5       |
| Phoenix                    | Hydrocortisone acetate | 1568/05131813    | 1       |
| Fagron                     | Hydrocortisone acetate | 15A03-B09-307133 | 1       |
| Großhandel                 | Hydrocortisone acetate | 157000           | 1       |
| Fagron                     | Hydrocortisone acetate | 15A03-B09-307300 | 1       |
| Caelo                      | Hydrocortisone acetate | 15A07-B03-306545 | 1       |
| Fagron                     | Hydrocortisone acetate | 15A07-B03-306545 | 1       |
| Phoenix                    | Hydrocortisone acetate | 15A30-B09        | 1       |
| Fagron                     | Hydrocortisone acetate | 15A30-B09-307090 | 1       |
| Fagron                     | Hydrocortisone acetate | 15A30-B09-307133 | 5       |
| Fagron                     | Hydrocortisone acetate | 15H24-B01        | 1       |
| Caelo                      | Hydrocortisone acetate | 15H24B01-316480  | 1       |
| Fagron                     | Hydrocortisone acetate | 15H24-B01-314236 | 1       |
| Caelo                      | Hydrocortisone acetate | 15H24-B01-314236 | 2       |
| Fagron                     | Hydrocortisone acetate | 15h24-b01-314236 | 1       |
| Fagron                     | Hydrocortisone acetate | 15H24-B01-316480 | 1       |
| Phoenix                    | Hydrocortisone acetate | 15J28-B12        | 1       |
| Fagron                     | Hydrocortisone acetate | 15J28-B12        | 1       |
| Fagron                     | Hydrocortisone acetate | 15J28-B12-317771 | 1       |
| Caelo                      | Hydrocortisone acetate | 1600406          | 1       |
| Caelo                      | Hydrocortisone acetate | 16004402         | 9       |
| Caelo                      | Hydrocortisone acetate | 160044003        | 1       |
| Caelo/Phoenix              | Hydrocortisone acetate | 16004402         | 1       |

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| Supplier                   | Substance              | Batch            | Spectra |
|----------------------------|------------------------|------------------|---------|
| Fagron                     | Hydrocortisone acetate | 16004402         | 1       |
| Caelo                      | Hydrocortisone acetate | 16004403         | 7       |
| Caelo                      | Hydrocortisone acetate | 16004405         | 5       |
| Caelo                      | Hydrocortisone acetate | 16004406         | 11      |
| Euro OTC                   | Hydrocortisone acetate | 16004406         | 1       |
| Caelo                      | Hydrocortisone acetate | 16004407         | 10      |
| AHD 07.03.2017 EK: 5,33    | Hydrocortisone acetate | 16004407         | 1       |
| Caelo                      | Hydrocortisone acetate | 16004408         | 6       |
| Euro OTC                   | Hydrocortisone acetate | 1604052-01       | 11      |
| Caelo                      | Hydrocortisone acetate | 1604052-01       | 3       |
| Euro OTC                   | Hydrocortisone acetate | 160405201        | 1       |
| Fagron                     | Hydrocortisone acetate | 160405201        | 1       |
| Caesar & Loretz GmbH Hi... | Hydrocortisone acetate | 16095404         | 1       |
| Caelo                      | Hydrocortisone acetate | 16095404         | 8       |
| Caesar & Loretz            | Hydrocortisone acetate | 16095404         | 1       |
| Caelo                      | Hydrocortisone acetate | 16095405         | 5       |
| Caelo                      | Hydrocortisone acetate | 16095406         | 10      |
| Caelo                      | Hydrocortisone acetate | 16095407         | 3       |
| Caelo                      | Hydrocortisone acetate | 16238704         | 2       |
| Caelo                      | Hydrocortisone acetate | 16238706         | 7       |
| Sanacorp                   | Hydrocortisone acetate | 16238706         | 1       |
| Caelo                      | Hydrocortisone acetate | 16238707         | 1       |
| Caesar&Loretz GmbH,Phön... | Hydrocortisone acetate | 16238708         | 1       |
| Caelo                      | Hydrocortisone acetate | 16238708         | 6       |
| Caelo                      | Hydrocortisone acetate | 16238709         | 2       |
| Gehe                       | Hydrocortisone acetate | 16238710         | 1       |
| Caelo                      | Hydrocortisone acetate | 16238710         | 1       |
| Sanacorp                   | Hydrocortisone acetate | 16238710         | 1       |
| Caelo                      | Hydrocortisone acetate | 16238712         | 5       |
| Caelo                      | Hydrocortisone acetate | 16238714         | 1       |
| Caelo                      | Hydrocortisone acetate | 166004407        | 1       |
| Fagron                     | Hydrocortisone acetate | 16H18-B04-325093 | 1       |
| Fagron                     | Hydrocortisone acetate | 16J28-B05        | 2       |
| Caelo                      | Hydrocortisone acetate | 16C15-B04-321459 | 1       |
| Fagron                     | Hydrocortisone acetate | 16H18-B04-327325 | 1       |
| Fagron                     | Hydrocortisone acetate | 16J28-B05-330083 | 1       |
| Caelo                      | Hydrocortisone acetate | 17086203         | 1       |
| Caelo                      | Hydrocortisone acetate | 27091403         | 1       |
| Caelo                      | Hydrocortisone acetate | 28071508         | 1       |
| Sanacorp                   | Hydrocortisone acetate |                  | 1       |
| Caelo                      | Hydrocortisone acetate | CH13291705       | 1       |
| Fagron                     | Hydrocortisone acetate | HC0024           | 1       |
| Gehe                       | Hydrocortisone acetate | HC0024           | 1       |
| Lihua/phönix               | Hydrocortisone acetate | K06A20140801M    | 1       |
| Fagron                     | Hydrocortisone acetate | M39171           | 1       |
| Fagron                     | Hydrocortisone acetate | NCEHAC130201     | 1       |
| Caelo                      | Hydrocortisone acetate | P156/14          | 1       |
| Fagron                     | Hydrocortisone acetate | NCEHAC120701     | 1       |
| Caelo                      | Hydrocortisone acetate | 213E-01719       | 1       |
| Fagron                     | Hydrocortisone acetate | 8563642          | 1       |
| Euro OTC                   | Hydrocortisone acetate | 911I-01718       | 1       |
| Caelo                      | Hydrocortisone acetate | 7051303          | 1       |
| Caelo                      | Hydrocortisone acetate | 10083911         | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1010025-01       | 1       |
| Caelo                      | Hydrocortisone acetate | 10301904         | 1       |
| Caelo                      | Hydrocortisone acetate | 10301913         | 1       |
| Fagron                     | Hydrocortisone acetate | 11/01-N05        | 1       |
| Phönix                     | Hydrocortisone acetate | 1107004-01       | 1       |
| Euro OTC                   | Hydrocortisone acetate | 1107004-02       | 2       |
| ANZAG 16.04.2012           | Hydrocortisone acetate | 1107004-03       | 1       |

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| <b>Supplier</b>            | <b>Substance</b>       | <b>Batch</b> | <b>Spectra</b> |
|----------------------------|------------------------|--------------|----------------|
| Euro OTC                   | Hydrocortisone acetate | 1107004-03   | 5              |
| Sanacorp                   | Hydrocortisone acetate | 1107004-03   | 1              |
| Phönix                     | Hydrocortisone acetate | 110700403    | 1              |
| EuRho                      | Hydrocortisone acetate | 1107004-03   | 1              |
| Caelo                      | Hydrocortisone acetate | 11098604     | 1              |
| Gehe                       | Hydrocortisone acetate | 11098607     | 1              |
| Caelo                      | Hydrocortisone acetate | 11098611     | 1              |
| Caelo                      | Hydrocortisone acetate | 11098612     | 1              |
| Caelo                      | Hydrocortisone acetate | 11098615     | 1              |
| Fagron                     | Hydrocortisone acetate | 1112031      | 1              |
| Euro OTC                   | Hydrocortisone acetate | 1112031-01   | 14             |
| Phönix                     | Hydrocortisone acetate | 1112031-01   | 1              |
| Phönix, 27.04.2013         | Hydrocortisone acetate | 1112031-01   | 1              |
| Klenk                      | Hydrocortisone acetate | 1112031-01   | 1              |
| Noweda                     | Hydrocortisone acetate | 1112031-02   | 1              |
| Anzag                      | Hydrocortisone acetate | 1112031-02   | 2              |
| Anzag 01.02.2013           | Hydrocortisone acetate | 1112031-02   | 1              |
| Großhandel                 | Hydrocortisone acetate | 1112031-02   | 1              |
| Caelo                      | Hydrocortisone acetate | 1112031-02   | 1              |
| Phoenix 02.05.2013         | Hydrocortisone acetate | 1112031-02   | 1              |
| Caelo                      | Hydrocortisone acetate | 1113E-01718  | 1              |
| Caelo                      | Hydrocortisone acetate | 11263902     | 1              |
| Caelo                      | Hydrocortisone acetate | 11263905     | 1              |
| Kehr                       | Hydrocortisone acetate | 11263906     | 1              |
| Anzag 17.03.2012           | Hydrocortisone acetate | 11263905     | 1              |
| Caelo                      | Hydrocortisone acetate | 11263906     | 1              |
| Caelo                      | Hydrocortisone acetate | 11263907     | 1              |
| Caelo                      | Hydrocortisone acetate | 11263911     | 1              |
| Noweda                     | Hydrocortisone acetate | 11263912     | 1              |
| Caelo                      | Hydrocortisone acetate | 11263913     | 2              |
| Sanacorp                   | Hydrocortisone acetate | 11263913     | 1              |
| Kehr                       | Hydrocortisone acetate | 11263914     | 1              |
| Caelo                      | Hydrocortisone acetate | 11263914     | 1              |
| Caelo                      | Hydrocortisone acetate | 11263915     | 2              |
| Caelo                      | Hydrocortisone acetate | 11263916     | 4              |
| Caelo                      | Hydrocortisone acetate | 11263917     | 3              |
| Noweda                     | Hydrocortisone acetate | 11F24-N12    | 1              |
| Caelo                      | Hydrocortisone acetate | 12008402     | 4              |
| Caelo                      | Hydrocortisone acetate | 12008403     | 2              |
| Caelo                      | Hydrocortisone acetate | 12008404     | 4              |
| Gehe                       | Hydrocortisone acetate | 12008405     | 1              |
| Caelo                      | Hydrocortisone acetate | 12008405     | 5              |
| Caelo                      | Hydrocortisone acetate | 12008411     | 1              |
| Noweda/ Pharmacia & Upj... | Hydrocortisone acetate | 1205034-01   | 1              |
| Großhandel                 | Hydrocortisone acetate | 1205034-01   | 5              |
| Phoenix                    | Hydrocortisone acetate | 1205034-01   | 1              |
| Phönix                     | Hydrocortisone acetate | 1205034-01   | 1              |
| AHD, 23.10.2013            | Hydrocortisone acetate | 1205034-01   | 1              |
| Gehe                       | Hydrocortisone acetate | 1205034-01   | 1              |
| Euro OTC                   | Hydrocortisone acetate | 120503401    | 3              |
| Caelo                      | Hydrocortisone acetate | 12182402     | 12             |
| Caelo                      | Hydrocortisone acetate | 1213M-01718  | 1              |
| Phoenix                    | Hydrocortisone acetate | 12182402     | 1              |
| Caelo                      | Hydrocortisone acetate | 12182403     | 6              |
| Herbasinica                | Hydrocortisone acetate | 12182403     | 1              |
| Caelo                      | Hydrocortisone acetate | 12182404     | 22             |
| Sanacorp                   | Hydrocortisone acetate | 12182404     | 2              |
| Fagron                     | Hydrocortisone acetate | 12182404     | 1              |
| Kehr                       | Hydrocortisone acetate | 12182405     | 3              |
| Caesar&loretz,Phoenix      | Hydrocortisone acetate | 12182405     | 1              |

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| Supplier              | Substance              | Batch               | Spectra |
|-----------------------|------------------------|---------------------|---------|
| Caesar & Loretz GmbH  | Hydrocortisone acetate | 12182405            | 1       |
| Phönix Gotha          | Hydrocortisone acetate | 12182405            | 1       |
| Caelo                 | Hydrocortisone acetate | 12182408            | 2       |
| Caelo                 | Hydrocortisone acetate | 12183403            | 1       |
| Caelo                 | Hydrocortisone acetate | 12248501            | 1       |
| Nachprüfung           | Hydrocortisone acetate |                     | 1       |
| Phönix Gotha          | Hydrocortisone acetate | 12330103            | 1       |
| Caelo                 | Hydrocortisone acetate | 12330103            | 11      |
| Sanacorp              | Hydrocortisone acetate | 12330103            | 1       |
| Caesar&loretz,Phoenix | Hydrocortisone acetate | 12330103            | 1       |
| Caelo                 | Hydrocortisone acetate | 12330104            | 11      |
| Caelo                 | Hydrocortisone acetate | 12330105            | 4       |
| Caelo                 | Hydrocortisone acetate | 12330106            | 6       |
| Caelo                 | Hydrocortisone acetate | 12330107            | 10      |
| Pönix 26.06.2013      | Hydrocortisone acetate | 12330107            | 1       |
| Fagron                | Hydrocortisone acetate | 12330107            | 1       |
| Phoenix               | Hydrocortisone acetate | 12330107            | 1       |
| Phönix Gotha          | Hydrocortisone acetate | 12330108            | 1       |
| Caelo                 | Hydrocortisone acetate | 12330110            | 4       |
| Caelo                 | Hydrocortisone acetate | 12330113            | 3       |
| Caelo                 | Hydrocortisone acetate | 12330114            | 1       |
| Gehe                  | Hydrocortisone acetate | 1233015             | 1       |
| Fagron                | Hydrocortisone acetate | 12A13-N02           | 1       |
| Caelo                 | Hydrocortisone acetate | 1233016             | 1       |
| Phönix                | Hydrocortisone acetate | 12A13-N02           | 1       |
| Phönix                | Hydrocortisone acetate | 12K15-No4           | 1       |
| Caelo                 | Hydrocortisone acetate | 1315304             | 1       |
| FARGON                | Hydrocortisone acetate | 12k15-n04           | 1       |
| Caelo                 | Hydrocortisone acetate | 13155302            | 8       |
| Sanacorp              | Hydrocortisone acetate | 13155302            | 2       |
| gehe                  | Hydrocortisone acetate | 13155302            | 2       |
| Caelo                 | Hydrocortisone acetate | 13155304            | 6       |
| Caeolo/Noweda         | Hydrocortisone acetate | 13155303            | 1       |
| Caelo                 | Hydrocortisone acetate | 131553080           | 1       |
| Fagron                | Hydrocortisone acetate | 13155311            | 1       |
| Fagron                | Hydrocortisone acetate | 13A03-N04           | 5       |
| Fagron                | Hydrocortisone acetate | 13B25-N04           | 2       |
| Fagron                | Hydrocortisone acetate | 13E31-N02           | 3       |
| Fagron                | Hydrocortisone acetate | 13E31-No2           | 1       |
| Caelo                 | Hydrocortisone acetate | 1403903             | 1       |
| Sanacorp              | Hydrocortisone acetate | 14043903            | 1       |
| Euro OTC              | Hydrocortisone acetate | 140900502           | 1       |
| Caelo                 | Hydrocortisone acetate | 1406211718          | 1       |
| Caelo                 | Hydrocortisone acetate | 15061207            | 1       |
| Caelo                 | Hydrocortisone acetate | 17011402            | 1       |
| Caelo                 | Hydrocortisone acetate | 18011304            | 1       |
| Caelo                 | Hydrocortisone acetate | 20220911-3          | 1       |
| Caelo                 | Hydrocortisone acetate | 25101201            | 1       |
| Caelo                 | Hydrocortisone acetate | 2612M01718          | 1       |
| Caelo                 | Hydrocortisone acetate | 27091307            | 1       |
| Bombastus             | Hydrocortisone acetate | 2712M01718          | 1       |
| Caelo                 | Hydrocortisone acetate | 3110491             | 1       |
| Fagron                | Hydrocortisone acetate | 3613A-01718         | 1       |
| Caelo                 | Hydrocortisone acetate |                     | 1       |
| Euro OTC              | Hydrocortisone acetate | HCAZ11004K          | 2       |
| Phönix                | Hydrocortisone acetate | AKD8                | 1       |
| Noweda                | Hydrocortisone acetate | HCA003/0611         | 1       |
| Fagron                | Hydrocortisone acetate | 12008411            | 3       |
| AHD                   | Hydrocortisone acetate | 1205034-01          | 1       |
| Caelo                 | Hydrocortisone acetate | 12330111-3507411061 | 1       |

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| Supplier | Substance              | Batch    | Spectra |
|----------|------------------------|----------|---------|
| Fagron   | Hydrocortisone acetate | 12330114 | 1       |

- 68 444 spectra from 414 *Apo-Ident* customers from a total of 23 571 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hydrocortisone acetate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hydrocortisone acetate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 219           | 0              | 71 167        |
| <b>Type B</b> | 0              | 445           | 0              | 146 284       |
| <b>Type C</b> | 0              | 1048          | 141            | 68 444        |

The substance/substance group *Hydrocortisone acetate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.2603 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.6517 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 88.1413 % (> 87.8890 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21295     | 21889               | 3.75                         | 29.40                           |
| 21889     | 21889               | 0.00                         | 26.82                           |
| 22241     | 21889               | 4.33                         | 30.25                           |
| 22564     | 22564               | 0.00                         | 33.68                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Hydrocortisone butyrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21531-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Hydrocortisone butyrate; Hydrocortisoni butyras micronisatum

### Special notes

When selecting the *Hydrocortisone butyrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hydrocortisone butyrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Hydrocortisone b... | 13I26-N01        | 21531     | 40      | AR-15-FG-000944-01 |
| Fagron   | Hydrocortisone b... | 14D23-B01-296716 | 21723     | 30      | 20140509           |
| Fagron   | Hydrocortisone b... | 13I26-N01        | 21797     | 40      | 20130920           |
| Fagron   | Hydrocortisone b... | 16F20-B05-323903 | 23182     | 40      | 20160805           |
| Fagron   | Hydrocortisone b... | 13I26-N01        | 21797SI   | 30      | 20130920           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 180 spectra of 5 reference samples from the substance/substance group *Hydrocortisone butyrate*. These samples are listed above in the [calibration samples](#) section.
- 71 206 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 153 spectra of 6 reference samples from the substance/substance group *Hydrocortisone butyrate*.

| Supplier | Substance               | Batch            | Sample ID            | Spectra |
|----------|-------------------------|------------------|----------------------|---------|
| Fagron   | Hydrocortisone butyrate | 13I26-N01        | 21531 <sup>†</sup>   | 20      |
| Fagron   | Hydrocortisone butyrate | 14D23-B01-296716 | 21723 <sup>†</sup>   | 30      |
| Fagron   | Hydrocortisone butyrate | 13I26-N01        | 21797 <sup>†</sup>   | 20      |
| Fagron   | Hydrocortisone butyrate | 14D23-B01-296716 | 21723SI              | 48      |
| Fagron   | Hydrocortisone butyrate | 13I26-N01        | 21797SI <sup>†</sup> | 15      |
| Fagron   | Hydrocortisone butyrate | 16F20-B05-323903 | 23182SI              | 20      |

- 146 576 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Hydrocortisone butyrate*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance               | Batch            | Spectra |
|----------|-------------------------|------------------|---------|
| Fagron   | Hydrocortisone butyrate | 15G08-B16-314883 | 1       |

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hydrocortisone butyrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hydrocortisone butyrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 180           | 0              | 71 206        |
| <b>Type B</b> | 0              | 153           | 0              | 146 576       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Hydrocortisone butyrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.6667 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.0784 %) |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21531     | 21531               | 0.00                         | 24.27                           |
| 21723     | 21531               | 9.41                         | 32.46                           |
| 21797     | 21531               | 4.41                         | 30.46                           |
| 23182     | 21531               | 11.15                        | 32.34                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Hydroquinone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20091-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Hydroquinone; Hydrochinonum

### Special notes

When selecting the *Hydroquinone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hydroquinone*:

| Supplier | Substance    | Batch    | Sample ID | Spectra | Certificate        |
|----------|--------------|----------|-----------|---------|--------------------|
| Caelo    | Hydroquinone | 12288505 | 20884     | 40      | 20121015           |
| Caelo    | Hydroquinone | 14026904 | 21468     | 40      | 20140122           |
| Caelo    | Hydroquinone | 14281501 | 21791     | 40      | AR-15-FG-008058-01 |
| Caelo    | Hydroquinone | 14280110 | 21923     | 40      | 20141017           |
| Caelo    | Hydroquinone | 15057004 | 21975     | 40      | 20150306           |
| Caelo    | Hydroquinone | 15057001 | 22324     | 40      | 20150306           |
| Caelo    | Hydroquinone | 15057001 | 22351     | 40      | 20150306           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 280 spectra of 7 reference samples from the substance/substance group *Hydroquinone*. These samples are listed above in the [calibration samples](#) section.
- 71 106 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 8 reference samples from the substance/substance group *Hydroquinone*.

| Supplier | Substance    | Batch    | Sample ID          | Spectra |
|----------|--------------|----------|--------------------|---------|
| Caelo    | Hydroquinone | 14026904 | 21468 <sup>†</sup> | 20      |
| Caelo    | Hydroquinone | 14281501 | 21791 <sup>†</sup> | 20      |
| Caelo    | Hydroquinone | 14280110 | 21923 <sup>†</sup> | 20      |
| Caelo    | Hydroquinone | 15057004 | 21975 <sup>†</sup> | 20      |
| Caelo    | Hydroquinone | 15057001 | 22324 <sup>†</sup> | 20      |
| Caelo    | Hydroquinone | 15057001 | 22351 <sup>†</sup> | 20      |
| Caelo    | Hydroquinone | 16023105 | 23114              | 40      |
| Caelo    | Hydroquinone | 172215   | 23654              | 40      |

- 146 529 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 149 spectra from 99 *Apo-Ident* customers from 45 batches from the substance/substance group *Hydroquinone*.

| Supplier                   | Substance    | Batch              | Spectra |
|----------------------------|--------------|--------------------|---------|
| Caelo                      | Hydroquinone | 11163905           | 4       |
| Caelo                      | Hydroquinone | 12288502           | 2       |
| Alliance Healthcare        | Hydroquinone | 12288503           | 2       |
| Caelo                      | Hydroquinone | 13105405           | 8       |
| Phönix                     | Hydroquinone | 13105408           | 1       |
| Caelo                      | Hydroquinone | 13105408           | 6       |
| Apomix/Noweda              | Hydroquinone | 13105408           | 1       |
| Caelo                      | Hydroquinone | 14026902           | 5       |
| Caelo                      | Hydroquinone | 14180401           | 2       |
| Caelo                      | Hydroquinone | 14180410           | 3       |
| Caelo                      | Hydroquinone | 14180406           | 3       |
| Caesar & Loretz GmbH       | Hydroquinone | 14280104           | 1       |
| Caelo                      | Hydroquinone | 14280104           | 2       |
| Caelo                      | Hydroquinone | 14280105           | 1       |
| Gehe/Gehe                  | Hydroquinone | 14280110           | 1       |
| Caelo                      | Hydroquinone | 14280110           | 1       |
| Caelo                      | Hydroquinone | 14281501           | 7       |
| Phoenix Goettin            | Hydroquinone | 14281501           | 1       |
| Caelo                      | Hydroquinone | 14281507           | 4       |
| Caelo                      | Hydroquinone | 15057001           | 9       |
| Caelo                      | Hydroquinone | 15057004           | 6       |
| Euro/Sanacorp              | Hydroquinone | 15057004           | 1       |
| Caelo                      | Hydroquinone | 15057010           | 8       |
| Sanacorp                   | Hydroquinone | 16023103           | 1       |
| Caelo                      | Hydroquinone | 16023105           | 1       |
| Caelo                      | Hydroquinone | 16023112           | 2       |
| Caelo                      | Hydroquinone | 16051502           | 1       |
| Caelo                      | Hydroquinone | 18031403           | 1       |
| Caelo                      | Hydroquinone | 21102014A          | 1       |
| Caelo                      | Hydroquinone |                    | 1       |
| Caelo                      | Hydroquinone | 52840166           | 1       |
| Caelo                      | Hydroquinone | 10145101           | 1       |
| Fagron                     | Hydroquinone |                    | 1       |
| Caelo                      | Hydroquinone | 10145103           | 1       |
| Caelo                      | Hydroquinone | 10145113           | 2       |
| Caelo                      | Hydroquinone | 11163907           | 5       |
| Caelo                      | Hydroquinone | 11163912           | 4       |
| Caesar & Loretz GmbH, 4. . | Hydroquinone | 11163912           | 1       |
| Caelo                      | Hydroquinone | 11163912/Int312052 | 1       |
| Caelo                      | Hydroquinone | 1163902            | 1       |
| Sanacorp                   | Hydroquinone | 12156703           | 1       |
| Caelo                      | Hydroquinone | 12156705           | 5       |
| Gehe                       | Hydroquinone | 12156706           | 2       |
| Caelo                      | Hydroquinone | 12156706           | 1       |
| Anzag 22.02.2013           | Hydroquinone | 12288503           | 1       |
| Sanacorp                   | Hydroquinone | 12288503           | 1       |
| Caelo                      | Hydroquinone | 12288503           | 2       |
| Caelo                      | Hydroquinone | 12288505           | 8       |
| Anzag                      | Hydroquinone | 12288505           | 2       |
| A.H. 14.06.13 ek: 3,97EUR  | Hydroquinone | 12288505           | 1       |
| Caelo                      | Hydroquinone | 13105402           | 9       |
| AHD                        | Hydroquinone | 13105405           | 1       |
| Caesar & Loretz GmbH       | Hydroquinone | 13105405           | 1       |
| Caelo                      | Hydroquinone | 14121202           | 1       |
| Caelo                      | Hydroquinone | 72265417           | 1       |
| Caelo                      | Hydroquinone | 20200712-3         | 1       |
| 14026902                   | Hydroquinone | InterneCharge1214Q | 1       |

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| Supplier | Substance    | Batch    | Spectra |
|----------|--------------|----------|---------|
| Anzag    | Hydroquinone | 11163912 | 1       |
| Anzag    | Hydroquinone | 12156705 | 1       |
| Caelo    | Hydroquinone | 1228503  | 1       |
| Caelo    | Hydroquinone | 12285201 | 1       |
| Caelo    | Hydroquinone | 1263912  | 1       |

- 69 484 spectra from 414 *Apo-Ident* customers from a total of 23 758 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hydroquinone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hydroquinone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 280           | 0              | 71 106        |
| <b>Type B</b> | 0              | 200           | 0              | 146 529       |
| <b>Type C</b> | 0              | 148           | 1              | 69 484        |

The substance/substance group *Hydroquinone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.8571 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 99.3289 % (> 97.3154 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:



| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20884     | 21791               | 2.83                         | 25.35                           |
| 21468     | 21791               | 3.43                         | 22.96                           |
| 21791     | 21791               | 0.00                         | 23.71                           |
| 21923     | 21791               | 3.14                         | 23.63                           |
| 21975     | 21791               | 1.55                         | 22.84                           |
| 22324     | 21791               | 1.82                         | 23.45                           |
| 22351     | 21791               | 3.50                         | 22.18                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

IdentModul 1.3-2018-01

Validated substance/substance group **Hydroxyethylcelluloses (300 / 9000 mPa · s)**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20791-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

## Relevant substance names

Hydroxyethylcelluloses (300 / 9000 mPa · s); Hydroxyethylcellulose (apparent viscosity 300 mPas); Hydroxyethylcellulose (apparent viscosity 9000 mPas); Hydroxyethylcellulose (nominal viscosity 300 mPas); Hydroxyethylcellulose (nominal viscosity 9000 mPas); Hydroxyethylcellulosum G 300; Hydroxyethylcellulosum H 300; Hydroxyethylcellulosum HX

## Special notes

When selecting the *Hydroxyethylcelluloses (300 / 9000 mPa · s)* substance/substance group, the following information is displayed to the user:

*no information*

## Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

## Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

## Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hydroxyethylcelluloses (300 / 9000 mPa · s)*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Caelo    | Hydroxyethylcell... | 12249204   | 20791     | 40      | 20120830    |
| Euro OTC | Hydroxyethylcell... | 1110024-04 | 20792     | 40      | 20120110    |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Caelo    | Hydroxyethylcell... | 03936475         | 20862     | 20      | 20121001           |
| Fagron   | Hydroxyethylcell... | 13H22-N11        | 20908     | 40      | 20130826           |
| Caelo    | Hydroxyethylcell... | 13378506         | 21365     | 40      | 1507205            |
| Caelo    | Hydroxyethylcell... | 14352504         | 21792     | 40      | AR-15-FG-009318-01 |
| Caelo    | Hydroxyethylcell... | 161006           | 22459     | 40      | 20160426*          |
| Fagron   | Hydroxyethylcell... | 16E09-B05-327042 | 23102     | 40      | 20160530           |
| Caelo    | Hydroxyethylcell... | 16252008         | 23708     | 40      | 20160907           |
| Caelo    | Hydroxyethylcell... | 16278705         | 23710     | 40      | 20161014           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 380 spectra of 10 reference samples from the substance/substance group *Hydroxyethylcelluloses* (300 / 9000 mPa · s). These samples are listed above in the [calibration samples](#) section.
- 71 006 spectra from a total of 1542 batches from further 373 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 330 spectra of 9 reference samples from the substance/substance group *Hydroxyethylcelluloses* (300 / 9000 mPa · s).

| Supplier    | Substance                       | Batch      | Sample ID          | Spectra |
|-------------|---------------------------------|------------|--------------------|---------|
| zu erfassen | Hydroxyethylcellulose (appar... | pending    | 20146              | 40      |
| Caelo       | Hydroxyethylcellulose (appar... | 9312308    | 20184              | 50      |
| Euro OTC    | Hydroxyethylcellulose (appar... | 1101022-02 | 20238              | 40      |
| Caelo       | Hydroxyethylcellulose (appar... | 14352504   | 21792 <sup>†</sup> | 20      |
| Caelo       | Hydroxyethylcellulose (appar... | 161006     | 22459 <sup>†</sup> | 20      |
| Euro OTC    | Hydroxyethylcellulose (appar... | 1606030    | 22698              | 40      |
| Caelo       | Hydroxyethylcellulose (appar... | 16012909   | 22809              | 40      |
| Euro OTC    | Hydroxyethylcellulose (appar... | 1610039    | 22870              | 40      |
| Caelo       | Hydroxyethylcellulose (appar... | 16252003   | 23584              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*).

- 146 399 spectra from a total of 3186 batches from further 861 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 798 spectra from 253 *Apo-Ident* customers from 210 batches from the substance/substance group *Hydroxyethylcelluloses (300 / 9000 mPa · s)*.

| Supplier                   | Substance                       | Batch       | Spectra |
|----------------------------|---------------------------------|-------------|---------|
| Euro OTC                   | Hydroxyethylcellulose (appar... | 3081603     | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 914E-03301  | 1       |
| Gutenberg-Apotheke         | Hydroxyethylcellulose (appar... | 10019402    | 2       |
| Gutenberg-Apotheke         | Hydroxyethylcellulose (appar... | 11048105    | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1110024-04  | 20      |
| Caelo                      | Hydroxyethylcellulose (appar... | 12156907    | 11      |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 12175708    | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12274702    | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12369711    | 5       |
| Nachprüfung 2797           | Hydroxyethylcellulose (appar... | 12249202    | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1304008-01  | 28      |
| Gehe/EuRho                 | Hydroxyethylcellulose (appar... | 1304008-01  | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1304008-02  | 23      |
| Caelo                      | Hydroxyethylcellulose (appar... | 13041502    | 1       |
| Ashland / Noweda           | Hydroxyethylcellulose (appar... | 1304008-02  | 2       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1304008-02  | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 13072015A   | 1       |
| Ashland / Phoenix          | Hydroxyethylcellulose (appar... | 13090020-01 | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1309020     | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1309020-01  | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1309020-01  | 23      |
| Großhandel                 | Hydroxyethylcellulose (appar... | 1309020-01  | 1       |
| Fagron                     | Hydroxyethylcellulose (appar... | 1309020-01  | 2       |
| VDL20.05.14                | Hydroxyethylcellulose (appar... | 1309020-01  | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 130902001   | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1309020-01  | 1       |
| Phoenix 10.07.2014         | Hydroxyethylcellulose (appar... | 1309020-01  | 1       |
| Sanacorp/Phoenix           | Hydroxyethylcellulose (appar... | 1309020-01  | 1       |
| Defektur                   | Hydroxyethylcellulose (appar... | 1309020-01  | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1309020-02  | 6       |
| Alliance Healthcare/Hed... | Hydroxyethylcellulose (appar... | 1309020-02  | 1       |
| Fagron                     | Hydroxyethylcellulose (appar... | 130902002   | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1309020-02  | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1309020-03  | 10      |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 13099020-01 | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 13153505    | 10      |
| Caelo                      | Hydroxyethylcellulose (appar... | 1315306     | 1       |
| Gehe 24.06.2014            | Hydroxyethylcellulose (appar... | 13153505    | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 13153511    | 8       |
| Caelo                      | Hydroxyethylcellulose (appar... | 13182702    | 7       |

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Hence, these spectra are not independent and are not of *Type B*.

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| Supplier         | Substance                       | Batch               | Spectra |
|------------------|---------------------------------|---------------------|---------|
| Noweda           | Hydroxyethylcellulose (appar... | 13153511            | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 1337807             | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 1337808             | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 13378502            | 6       |
| Caelo            | Hydroxyethylcellulose (appar... | 133785              | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 13378506            | 3       |
| Caelo            | Hydroxyethylcellulose (appar... | 13378507            | 9       |
| gehe             | Hydroxyethylcellulose (appar... | 13378507            | 2       |
| Noweda           | Hydroxyethylcellulose (appar... | 13378507            | 1       |
| Caesar/Noweda    | Hydroxyethylcellulose (appar... | 13378507            | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 13378508            | 3       |
| Caelo            | Hydroxyethylcellulose (appar... | 13378510            | 3       |
| Caelo            | Hydroxyethylcellulose (appar... | 13378515            | 5       |
| Caelo            | Hydroxyethylcellulose (appar... | 13378516            | 3       |
| Caelo            | Hydroxyethylcellulose (appar... | 13378518            | 3       |
| Caelo            | Hydroxyethylcellulose (appar... | 13378524            | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 13378525            | 2       |
| Caelo            | Hydroxyethylcellulose (appar... | 13H22-N11           | 1       |
| Th. Geyer        | Hydroxyethylcellulose (appar... | 13L04-B03           | 1       |
| Fagron           | Hydroxyethylcellulose (appar... | 13L04-B03           | 2       |
| Phönix           | Hydroxyethylcellulose (appar... | 13L04-B03-289115    | 2       |
| Ashland Ind/Gehe | Hydroxyethylcellulose (appar... | 140017-01           | 1       |
| Fagron           | Hydroxyethylcellulose (appar... | 14/04-B05-300231    | 1       |
| Fagron           | Hydroxyethylcellulose (appar... | 1404-B05-300231     | 1       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1406017             | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 1406017-01          | 3       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1406017-01          | 1       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1406017-01          | 31      |
| Gehe             | Hydroxyethylcellulose (appar... | 1406017-01          | 1       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1406017-02          | 27      |
| Caelo            | Hydroxyethylcellulose (appar... | 1406017-02          | 2       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1406017-03          | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 14095901            | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 140617-02           | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 14095905            | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 14095911            | 3       |
| Caelo            | Hydroxyethylcellulose (appar... | 14256002            | 2       |
| Caelo            | Hydroxyethylcellulose (appar... | 14352508            | 1       |
| Caelo            | Hydroxyethylcellulose (appar... | 14352510            | 3       |
| Caelo            | Hydroxyethylcellulose (appar... | 14352515            | 2       |
| Fagron           | Hydroxyethylcellulose (appar... | 14D04-B02-293558    | 2       |
| Fagron           | Hydroxyethylcellulose (appar... | 14D04-B02           | 2       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1496017-02          | 1       |
| Fagron           | Hydroxyethylcellulose (appar... | 14D04B02293555      | 1       |
| Fagron           | Hydroxyethylcellulose (appar... | 14F04-B06-295130    | 1       |
| Phoenix Goettin  | Hydroxyethylcellulose (appar... | 14F04-B06-295130    | 1       |
| Fagron           | Hydroxyethylcellulose (appar... | 14F04-B06-29784K137 | 1       |
| Fagron           | Hydroxyethylcellulose (appar... | 14F04-B06-297846    | 1       |
| Fagron           | Hydroxyethylcellulose (appar... | 14i04-b05-309049    | 1       |
| Fagron           | Hydroxyethylcellulose (appar... | 14I04-B05-300224    | 2       |
| Fagron           | Hydroxyethylcellulose (appar... | 14I04-B05           | 2       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1500418-02          | 1       |
| Fagron           | Hydroxyethylcellulose (appar... | 14Io4-B05           | 1       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1504018-01          | 10      |
| Castor/Phönix    | Hydroxyethylcellulose (appar... | 1504018-01          | 1       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1504018-02          | 18      |
| Fagron           | Hydroxyethylcellulose (appar... | 1504018-02          | 1       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1504018-03          | 1       |
| Euro OTC         | Hydroxyethylcellulose (appar... | 1504018-03          | 12      |
| Caelo            | Hydroxyethylcellulose (appar... | 1504018-1           | 1       |

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| Supplier                  | Substance                       | Batch            | Spectra |
|---------------------------|---------------------------------|------------------|---------|
| Euro OTC                  | Hydroxyethylcellulose (appar... | 1504019-02       | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 15086403         | 5       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | 150418-01        | 1       |
| Fagron                    | Hydroxyethylcellulose (appar... | 15086403         | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 15086405         | 8       |
| Caelo                     | Hydroxyethylcellulose (appar... | 15086407         | 6       |
| Fagron                    | Hydroxyethylcellulose (appar... | 15086407         | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 15086408         | 2       |
| Caelo                     | Hydroxyethylcellulose (appar... | 15086503         | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 15086504         | 3       |
| Caelo                     | Hydroxyethylcellulose (appar... | 15086505         | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 15086506         | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 15086507         | 3       |
| Caelo                     | Hydroxyethylcellulose (appar... | 15199501         | 5       |
| Jenne                     | Hydroxyethylcellulose (appar... | 15199501         | 1       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | 154018-02        | 1       |
| Fagron                    | Hydroxyethylcellulose (appar... | 15B04-B03-312859 | 2       |
| Fagron                    | Hydroxyethylcellulose (appar... | 15B04-B03-315495 | 1       |
| Fagron                    | Hydroxyethylcellulose (appar... | 15E07-B05-316511 | 2       |
| Fagron                    | Hydroxyethylcellulose (appar... | 15H28-B10        | 1       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | 1610039-01       | 5       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16012909         | 1       |
| Fagron                    | Hydroxyethylcellulose (appar... | 15H28-B10-319028 | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 1606030-01       | 5       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | 1606030-01       | 18      |
| Caelo                     | Hydroxyethylcellulose (appar... | 160603001        | 1       |
| apo-ident.                | Hydroxyethylcellulose (appar... | 1606030-02       | 1       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | 1606030-02       | 5       |
| Fiebig                    | Hydroxyethylcellulose (appar... | 1606030-02       | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100604         | 5       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100605         | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100606         | 11      |
| Ebert & Jacobi 02.08.2016 | Hydroxyethylcellulose (appar... | 16100606         | 1       |
| Phönix                    | Hydroxyethylcellulose (appar... | 16100606         | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100612         | 4       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100607         | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100610         | 2       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100613         | 4       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100615         | 2       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100617         | 5       |
| Gehe                      | Hydroxyethylcellulose (appar... | 16100617         | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100622         | 2       |
| Caelo                     | Hydroxyethylcellulose (appar... | 16100625         | 2       |
| Fagron                    | Hydroxyethylcellulose (appar... | 16E09-B05-321320 | 2       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | 16603001         | 1       |
| Fagron                    | Hydroxyethylcellulose (appar... | 16L07-B04-331846 | 2       |
| Alliance Healthcare       | Hydroxyethylcellulose (appar... | 16L07-B04-331846 | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 19051406         | 1       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | 17042014A        | 1       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | 1909020-02       | 1       |
| Fagron                    | Hydroxyethylcellulose (appar... | 2178             | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 220914PML02      | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 4815A-03301      | 1       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | K1371            | 2       |
| Caelo                     | Hydroxyethylcellulose (appar... | AKD11            | 1       |
| Fagron                    | Hydroxyethylcellulose (appar... | K1373            | 2       |
| Ashland Industries/Anzag  | Hydroxyethylcellulose (appar... | L1891            | 1       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | 1110024-01       | 2       |
| Euro OTC                  | Hydroxyethylcellulose (appar... | N1535            | 1       |
| Caelo                     | Hydroxyethylcellulose (appar... | 11186202         | 2       |

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| Supplier                   | Substance                       | Batch                | Spectra |
|----------------------------|---------------------------------|----------------------|---------|
| Caelo                      | Hydroxyethylcellulose (appar... | 11266305             | 5       |
| Fagron                     | Hydroxyethylcellulose (appar... | 12C27-N01            | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 213I-03301           | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 2402212528           | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 314Q3301             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 8051305              | 1       |
| EuRho                      | Hydroxyethylcellulose (appar... | 3081202              | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 80616-3              | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 10019408             | 2       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1007018-01           | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1101022-02           | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 110505401            | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1108027-01           | 2       |
| Noweda                     | Hydroxyethylcellulose (appar... | 1108027-01           | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1110024-01           | 5       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1110024-01           | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1110024-02           | 13      |
| Phönix, 21.06.2012         | Hydroxyethylcellulose (appar... | 1110024-02           | 2       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1110024-02           | 2       |
| Anzag                      | Hydroxyethylcellulose (appar... | 1110024-03           | 3       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1110024-03           | 19      |
| Gehe                       | Hydroxyethylcellulose (appar... | 1110024-03           | 1       |
| Sanacorp                   | Hydroxyethylcellulose (appar... | 1110024-03           | 1       |
| Europharm/Otto             | Hydroxyethylcellulose (appar... | 1110024-03           | 1       |
| Phönix                     | Hydroxyethylcellulose (appar... | 111002403            | 1       |
| EuRho                      | Hydroxyethylcellulose (appar... | 1110024-03           | 1       |
| Holdermann                 | Hydroxyethylcellulose (appar... | 1110024-04           | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1110024-04           | 1       |
| Gehe                       | Hydroxyethylcellulose (appar... | 111002404            | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 111024-02            | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1110024-04-336431909 | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 11110024-03          | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1113E-03301          | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 11186221             | 2       |
| Caelo                      | Hydroxyethylcellulose (appar... | 11266316             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 11266317             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 11304601             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 11304619             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 11304614             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 11304620             | 4       |
| Fagron                     | Hydroxyethylcellulose (appar... | 11E09-N08            | 1       |
| Fagron                     | Hydroxyethylcellulose (appar... | 11I02-N02            | 2       |
| Fagron                     | Hydroxyethylcellulose (appar... | 11I02-N12            | 1       |
| Euro/Zentrum Apo           | Hydroxyethylcellulose (appar... | 1212N-03301          | 2       |
| Erika apotheke             | Hydroxyethylcellulose (appar... | 12156901             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12156902             | 1       |
| Sanacorp                   | Hydroxyethylcellulose (appar... | 12156901             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12156901             | 4       |
| Phönix                     | Hydroxyethylcellulose (appar... | 12156902             | 2       |
| Noweda                     | Hydroxyethylcellulose (appar... | 12156907             | 1       |
| Gehe                       | Hydroxyethylcellulose (appar... | 12156908             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12156908             | 5       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12156915             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 122492014            | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12249202             | 3       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12249204             | 3       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12249205             | 5       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12249216             | 7       |
| Caesar & Loretz GmbH D-... | Hydroxyethylcellulose (appar... | 12274702             | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12274710             | 2       |

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| Supplier                   | Substance                       | Batch            | Spectra |
|----------------------------|---------------------------------|------------------|---------|
| Caelo                      | Hydroxyethylcellulose (appar... | 12369704         | 12      |
| Fagron                     | Hydroxyethylcellulose (appar... | 12345            | 2       |
| Phönix                     | Hydroxyethylcellulose (appar... | 12369704         | 1       |
| Phönix                     | Hydroxyethylcellulose (appar... | 12369711         | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12369713         | 3       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12369717         | 2       |
| Caelo                      | Hydroxyethylcellulose (appar... | 12369718         | 1       |
| Gehe                       | Hydroxyethylcellulose (appar... | 12369718         | 1       |
| Fagron                     | Hydroxyethylcellulose (appar... | 12A09-N06        | 3       |
| Fagron                     | Hydroxyethylcellulose (appar... | 12C02-N06        | 1       |
| Fagron                     | Hydroxyethylcellulose (appar... | 12C27-N01        | 1       |
| Fagron                     | Hydroxyethylcellulose (appar... | 12H02-N06        | 2       |
| Sanacorp                   | Hydroxyethylcellulose (appar... | 12H02-N06        | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 13040008-02      | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 130400801        | 1       |
| Euroo/Phoenix              | Hydroxyethylcellulose (appar... | 1304008-01       | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1304008-01       | 1       |
| Ashland                    | Hydroxyethylcellulose (appar... | 130400801        | 1       |
| AHD, 28.11.13              | Hydroxyethylcellulose (appar... | 1304008-01       | 1       |
| Eurp                       | Hydroxyethylcellulose (appar... | 130400801        | 2       |
|                            | Hydroxyethylcellulose (appar... | 1304008-01       | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1304008-01       | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1304008-02       | 3       |
| Alliance Health 27.12.2... | Hydroxyethylcellulose (appar... | 1304008-02       | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 130400802        | 2       |
| Phonix                     | Hydroxyethylcellulose (appar... | 1309020-01       | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 130902001        | 1       |
| Ashland/Sanacorp           | Hydroxyethylcellulose (appar... | 1309020-01       | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 13153501         | 8       |
| Gehe                       | Hydroxyethylcellulose (appar... | 13153501         | 1       |
| Noweda                     | Hydroxyethylcellulose (appar... | 13153501         | 1       |
| Caesar & Loretz GmbH       | Hydroxyethylcellulose (appar... | 13153501         | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 13153502         | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 13153506         | 9       |
| AHD                        | Hydroxyethylcellulose (appar... | 13153511         | 1       |
| Fagron                     | Hydroxyethylcellulose (appar... | 13A18-N01        | 5       |
| Phönix                     | Hydroxyethylcellulose (appar... | 13378507         | 1       |
| Gehe                       | Hydroxyethylcellulose (appar... | 13A18-N01        | 1       |
| Fagron                     | Hydroxyethylcellulose (appar... | 13D26-N11        | 6       |
| Caelo                      | Hydroxyethylcellulose (appar... | 13D26-N11        | 2       |
| Fagron                     | Hydroxyethylcellulose (appar... | 13d26-n16        | 2       |
| Fagron                     | Hydroxyethylcellulose (appar... | 13H22-N11        | 8       |
| Caelo                      | Hydroxyethylcellulose (appar... | 140317           | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... | 1406212528       | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 20031305         | 1       |
| Kehr                       | Hydroxyethylcellulose (appar... | 211112PML01      | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 26071301         | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 26071212         | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 290114PML01      | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 4512I-03301      | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 5012I-03301      | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | AKD10            | 1       |
| Fagron                     | Hydroxyethylcellulose (appar... | J0696            | 2       |
| phönix,30.11.12            | Hydroxyethylcellulose (appar... | J0696            | 1       |
| Euro OTC                   | Hydroxyethylcellulose (appar... |                  | 2       |
| s.Prüfprotokoll            | Hydroxyethylcellulose (appar... |                  | 2       |
| Phönix                     | Hydroxyethylcellulose (appar... | 1304008-02       | 1       |
| Bombastus                  | Hydroxyethylcellulose (appar... | 14095911         | 1       |
| Caelo                      | Hydroxyethylcellulose (appar... | 1504018-02       | 1       |
| Fagron                     | Hydroxyethylcellulose (appar... | 14I04-B05-309049 | 1       |

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| Supplier | Substance                       | Batch       | Spectra |
|----------|---------------------------------|-------------|---------|
| Caelo    | Hydroxyethylcellulose (appar... | 16100620    | 2       |
| Caelo    | Hydroxyethylcellulose (appar... | 13182714    | 1       |
| Caelo    | Hydroxyethylcellulose (appar... | 213M-03301  | 1       |
| Caelo    | Hydroxyethylcellulose (appar... | 21011502    | 1       |
| Caelo    | Hydroxyethylcellulose (appar... | 31031402    | 1       |
| Gehe     | Hydroxyethylcellulose (appar... | 11266305    | 1       |
| Kehr     | Hydroxyethylcellulose (appar... | 110024-02   | 1       |
| Anzag    | Hydroxyethylcellulose (appar... | 12249204    | 1       |
| Caelo    | Hydroxyethylcellulose (appar... | 12274720    | 1       |
| Caelo    | Hydroxyethylcellulose (appar... | 19011302    | 1       |
| Caelo    | Hydroxyethylcellulose (appar... | 25071301    | 1       |
| Euro OTC | Hydroxyethylcellulose (appar... | 1613M-03301 | 1       |
| EuRho    | Hydroxyethylcellulose (appar... | 2512I-03301 | 1       |
| Euro OTC | Hydroxyethylcellulose (appar... | 130902003   | 1       |
| Caelo    | Hydroxyethylcellulose (appar... | 313Q-03301  | 1       |
| Euro OTC | Hydroxyethylcellulose (appar... | 1105054-01  | 1       |

- 68 835 spectra from 414 *Apo-Ident* customers from a total of 23 598 batches from a further 695 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hydroxyethylcelluloses* (300 / 9000 mPa · s) can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hydroxyethylcelluloses* (300 / 9000 mPa · s) and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 380           | 0              | 71 006        |
| <b>Type B</b> | 0              | 280           | 50             | 146 399       |
| <b>Type C</b> | 0              | 790           | 8              | 68 835        |

The substance/substance group *Hydroxyethylcelluloses* (300 / 9000 mPa · s) can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.4211 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 84.8485 % (> 83.9394 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 98.9975 % (> 98.6216 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20791     | 21792               | 13.46                        | 78.92                           |
| 20792     | 21792               | 9.19                         | 76.00                           |
| 20862     | 22459               | 8.59                         | 83.07                           |
| 20908     | 21365               | 11.68                        | 73.85                           |
| 21365     | 21365               | 0.00                         | 72.61                           |
| 21792     | 21792               | 0.00                         | 80.73                           |
| 22459     | 22459               | 0.00                         | 82.65                           |
| 23102     | 21792               | 7.65                         | 79.94                           |
| 23708     | 21792               | 1.60                         | 80.92                           |
| 23710     | 21792               | 9.32                         | 77.00                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Hydroxypropyl cellulose (300 mPa · s)**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20686-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Hydroxypropyl cellulose (300 mPa · s); Hydroxypropylcellulosum (300 mPa · s)

### Special notes

When selecting the *Hydroxypropyl cellulose (300 mPa · s)* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hydroxypropyl cellulose (300 mPa · s)*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate        |
|----------|---------------------|----------|-----------|---------|--------------------|
| Caelo    | Hydroxypropyl ce... | 12093107 | 20686     | 40      | 1402049            |
| Caelo    | Hydroxypropyl ce... | 14189804 | 21767     | 40      | AR-15-FG-014922-01 |
| Caelo    | Hydroxypropyl ce... | 15345001 | 22258     | 40      | 20151104           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Hydroxypropyl cellulose* (300 mPa · s). These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 3 reference samples from the substance/substance group *Hydroxypropyl cellulose* (300 mPa · s).

| Supplier | Substance                       | Batch    | Sample ID          | Spectra |
|----------|---------------------------------|----------|--------------------|---------|
| Caelo    | Hydroxypropyl cellulose (300... | 14189804 | 21767 <sup>†</sup> | 20      |
| Caelo    | Hydroxypropyl cellulose (300... | 15345001 | 22258 <sup>†</sup> | 20      |
| Caelo    | Hydroxypropyl cellulose (300... | 15345009 | 23123              | 40      |

- 146 649 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 4 spectra from 4 *Apo-Ident* customers from 4 batches from the substance/substance group *Hydroxypropyl cellulose* (300 mPa · s).

| Supplier | Substance                       | Batch    | Spectra |
|----------|---------------------------------|----------|---------|
| Caelo    | Hydroxypropyl cellulose (300... | 14189801 | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier | Substance                       | Batch    | Spectra |
|----------|---------------------------------|----------|---------|
| Caelo    | Hydroxypropyl cellulose (300... | 13031306 | 1       |
| Caelo    | Hydroxypropyl cellulose (300... | 15129707 | 1       |
| Caelo    | Hydroxypropyl cellulose (300... | 13031309 | 1       |

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hydroxypropyl cellulose (300 mPa · s)* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hydroxypropyl cellulose (300 mPa · s)* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 76            | 4              | 146 649       |
| <b>Type C</b> | 0              | 2             | 2              | 69 629        |

The substance/substance group *Hydroxypropyl cellulose (300 mPa · s)* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 95.0000 % (> 91.2500 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20686     | 20686               | 0.00                         | 16.76                           |
| 21767     | 21767               | 0.00                         | 17.78                           |
| 22258     | 21767               | 7.07                         | 22.12                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Hyoscine butylbromide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20766-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Hyoscine butylbromide; Butylscopolaminium bromatum; Hyoscini butylbromidum

### Special notes

When selecting the *Hyoscine butylbromide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hyoscine butylbromide*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Hyoscine butylbr... | 12K01-N07        | 20766     | 40      | 1406057     |
| Fagron   | Hyoscine butylbr... | 12K01-N07        | 20897     | 40      | 20121102    |
| Fagron   | Hyoscine butylbr... | 13K22-N03        | 21049     | 40      | 20131126    |
| Fagron   | Hyoscine butylbr... | 15I09-B04-312245 | 21954     | 40      | 20150921    |
| Fagron   | Hyoscine butylbr... | 15I09-B04-316806 | 22344     | 40      | 20150921    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Hyoscine butylbromide*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 132 spectra of 5 reference samples from the substance/substance group *Hyoscine butylbromide*.

| Supplier | Substance             | Batch            | Sample ID          | Spectra |
|----------|-----------------------|------------------|--------------------|---------|
| Fagron   | Hyoscine butylbromide | 15I09-B04-312245 | 21954 <sup>†</sup> | 20      |
| Fagron   | Hyoscine butylbromide | 15I09-B04-316806 | 22344 <sup>†</sup> | 20      |
| Fagron   | Hyoscine butylbromide | 16I20-B08-326942 | 22903              | 40      |
| Fagron   | Hyoscine butylbromide | 16I20-B08-326942 | 22937              | 40      |
| Fagron   | Hyoscine butylbromide | 16I20-B08-326942 | not required       | 12      |

- 146 597 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Hyoscine butylbromide*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hyoscine butylbromide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hyoscine butylbromide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 132           | 0              | 146 597       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Hyoscine butylbromide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.4545 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20766     | 20766               | 0.00                         | 78.06                           |
| 20897     | 20766               | 16.23                        | 82.30                           |
| 21049     | 20766               | 4.60                         | 78.01                           |
| 21954     | 20766               | 4.00                         | 77.04                           |
| 22344     | 20766               | 5.83                         | 76.80                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe

mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Hyoscine hydrobromide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21676-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Hyoscine hydrobromide; Scopolamini hydrobromidum

### Special notes

When selecting the *Hyoscine hydrobromide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Hyoscine hydrobromide*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Caelo    | Hyoscine hydrobr... | 14278801         | 21676     | 40      | 1504154     |
| Caelo    | Hyoscine hydrobr... | 15054501         | 21764     | 40      | 1511156     |
| Caelo    | Hyoscine hydrobr... | 15054504         | 21925     | 40      | 20150310    |
| Fagron   | Hyoscine hydrobr... | 15L09-B04-334706 | 23418     | 40      | 20151228    |
| Fagron   | Hyoscine hydrobr... | 15L09-B04-334706 | 23419     | 40      | 20151228    |
| Caelo    | Hyoscine hydrobr... | 15054501         | 21764SI   | 28      | 1511156     |
| Caelo    | Hyoscine hydrobr... | 15054504         | 21925SI   | 12      | 20150310    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 7 reference samples from the substance/substance group *Hyoscine hydrobromide*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 275 spectra of 9 reference samples from the substance/substance group *Hyoscine hydrobromide*.

| Supplier | Substance             | Batch            | Sample ID            | Spectra |
|----------|-----------------------|------------------|----------------------|---------|
| Caelo    | Hyoscine hydrobromide | 14278801         | 21676 <sup>†</sup>   | 45      |
| Caelo    | Hyoscine hydrobromide | 15054501         | 21764 <sup>†</sup>   | 20      |
| Caelo    | Hyoscine hydrobromide | 15054504         | 21925 <sup>†</sup>   | 20      |
| Caelo    | Hyoscine hydrobromide | 15054504         | 23441                | 30      |
| Caelo    | Hyoscine hydrobromide | 15054501         | 21764SI <sup>†</sup> | 32      |
| Caelo    | Hyoscine hydrobromide | 15054504         | 21925SI <sup>†</sup> | 18      |
| Fagron   | Hyoscine hydrobromide | 15L09-B04-334706 | 23418SI              | 30      |
| Fagron   | Hyoscine hydrobromide | 15L09-B04-334706 | 23419SI              | 40      |
| Caelo    | Hyoscine hydrobromide | 15054504         | 23441SI              | 40      |

- 146 454 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 2 spectra from 2 *Apo-Ident* customers from 2 batches from the substance/substance group *Hyoscine hydrobromide*.

| Supplier | Substance             | Batch    | Spectra |
|----------|-----------------------|----------|---------|
| Caelo    | Hyoscine hydrobromide | 14278801 | 1       |
| Caelo    | Hyoscine hydrobromide | 15054505 | 1       |

- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Hyoscine hydrobromide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Hyoscine hydrobromide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 223           | 52             | 146 454       |
| <b>Type C</b> | 0              | 2             | 0              | 69 631        |

The substance/substance group *Hyoscine hydrobromide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 81.0909 % (> 80.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21676     | 21676               | 0.00                         | 18.28                           |
| 21764     | 21764               | 0.00                         | 29.74                           |
| 21925     | 21764               | 18.08                        | 27.37                           |
| 23418     | 21764               | 8.97                         | 28.77                           |
| 23419     | 21764               | 5.63                         | 26.39                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ibuprofen**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20205-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ibuprofen; Ibuprofenum

### Special notes

When selecting the *Ibuprofen* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ibuprofen*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Caelo    | Ibuprofen | 11352219   | 20774     | 40      | 20120124    |
| Euro OTC | Ibuprofen | 1211011-02 | 21248     | 40      | 1501533     |
| Caelo    | Ibuprofen | 172271     | 23641     | 40      | 20170831*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Ibuprofen*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 3 reference samples from the substance/substance group *Ibuprofen*.

| Supplier | Substance | Batch      | Sample ID | Spectra |
|----------|-----------|------------|-----------|---------|
| Caelo    | Ibuprofen | 9111410    | 20205     | 40      |
| Caelo    | Ibuprofen | 13105108   | 21321     | 40      |
| Euro OTC | Ibuprofen | 1410025-02 | 23587     | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 19 spectra from 6 *Apo-Ident* customers from 6 batches from the substance/substance group *Ibuprofen*.

| Supplier | Substance | Batch      | Spectra |
|----------|-----------|------------|---------|
| Fagron   | Ibuprofen | 1012039-02 | 1       |

*continued on the next page*

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

continued from previous page

| Supplier | Substance | Batch      | Spectra |
|----------|-----------|------------|---------|
| Euro OTC | Ibuprofen | 1211011-01 | 1       |
| Caelo    | Ibuprofen |            | 1       |
| Caelo    | Ibuprofen | 1410025-01 | 3       |
| Euro OTC | Ibuprofen | 1410025-01 | 6       |
| Caelo    | Ibuprofen | 1410025-02 | 2       |
| Euro OTC | Ibuprofen | 1410025-02 | 4       |
| Caelo    | Ibuprofen | 15103014   | 1       |

- 69 614 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ibuprofen* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ibuprofen* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 84            | 36             | 146 609       |
| <b>Type C</b> | 0              | 18            | 1              | 69 614        |

The substance/substance group *Ibuprofen* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 70.0000 % (> 67.5000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20774     | 21248               | 9.21                         | 57.96                           |
| 21248     | 21248               | 0.00                         | 55.05                           |
| 23641     | 23641               | 0.00                         | 53.92                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

IdentModul 1.3-2018-01

Validated substance/substance group **Indomethacin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20720-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

## Relevant substance names

Indomethacin; Indometacinum

## Special notes

When selecting the *Indomethacin* substance/substance group, the following information is displayed to the user:

*no information*

## Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

## Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

## Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Indomethacin*:

| Supplier | Substance    | Batch      | Sample ID | Spectra | Certificate |
|----------|--------------|------------|-----------|---------|-------------|
| Euro OTC | Indomethacin | 1012009-02 | 20720     | 40      | 1402050     |
| Euro OTC | Indomethacin | 1205002-01 | 21327     | 40      | 20120521    |
| Euro OTC | Indomethacin | 1512031    | 22291     | 40      | 20160122*   |
| Euro OTC | Indomethacin | 1612017    | 22981     | 40      | 20170209*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Indomethacin*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *Indomethacin*.

| Supplier | Substance    | Batch            | Sample ID          | Spectra |
|----------|--------------|------------------|--------------------|---------|
| Euro OTC | Indomethacin | 1512031          | 22291 <sup>†</sup> | 20      |
| Fagron   | Indomethacin | 17I08-B06-339738 | 23715              | 40      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 5 spectra from 4 *Apo-Ident* customers from 2 batches from the substance/substance group *Indomethacin*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance    | Batch      | Spectra |
|----------|--------------|------------|---------|
| Euro OTC | Indomethacin | 1205002-01 | 2       |
| Euro OTC | Indomethacin | 1512031-01 | 2       |
| Gehe     | Indomethacin | 1512031-01 | 1       |

- 69 628 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Indomethacin* can be clearly distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Indomethacin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 5             | 0              | 69 628        |

The substance/substance group *Indomethacin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8815 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20720     | 20720               | 0.00                         | 63.20                           |
| 21327     | 22981               | 3.55                         | 66.76                           |
| 22291     | 22291               | 0.00                         | 65.47                           |
| 22981     | 22981               | 0.00                         | 60.47                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Inositol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20420-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Inositol; Inositolium; myo-Inositolium

### Special notes

When selecting the *Inositol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Inositol*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------|------------------|-----------|---------|--------------------|
| Euro OTC | Inositol  | 1206032-01       | 21280     | 40      | 20120814           |
| Fagron   | Inositol  | 13D15-B40-328250 | 23406     | 40      | AR-17-FG-016393-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Inositol*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 3 reference samples from the substance/substance group *Inositol*.

| Supplier | Substance | Batch            | Sample ID | Spectra |
|----------|-----------|------------------|-----------|---------|
| Euro OTC | Inositol  | 1011028-01       | 20420     | 40      |
| Euro OTC | Inositol  | L1507021-01      | 22797     | 40      |
| Fagron   | Inositol  | 13D15-B40-328250 | 23405     | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 10 spectra from 4 *Apo-Ident* customers from 5 batches from the substance/substance group *Inositol*.

| Supplier | Substance | Batch      | Spectra |
|----------|-----------|------------|---------|
| Euro OTC | Inositol  | 130400901  | 1       |
| Euro OTC | Inositol  | 1304009-01 | 3       |
| Euro OTC | Inositol  | 1206032-01 | 2       |
| Euro OTC | Inositol  | 1407006-01 | 3       |
| Fagron   | Inositol  | L13090200  | 1       |

- 69 623 spectra from 414 *Apo-Ident* customers from a total of 23 796 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Inositol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Inositol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 120           | 0              | 146 609       |
| <b>Type C</b> | 0              | 10            | 0              | 69 623        |

The substance/substance group *Inositol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21280     | 23406               | 3.65                         | 32.70                           |
| 23406     | 23406               | 0.00                         | 31.93                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das

alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Iodoform**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20094-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Iodoform; Iodoformium; Jodoformium

### Special notes

When selecting the *Iodoform* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Iodoform*:

| Supplier | Substance | Batch     | Sample ID | Spectra | Certificate        |
|----------|-----------|-----------|-----------|---------|--------------------|
| Fagron   | Iodoform  | 12L11-B41 | 21278     | 40      | 20140113           |
| Caelo    | Iodoform  | 12283206  | 21297     | 40      | 20130709           |
| Caelo    | Iodoform  | 16012302  | 23192     | 40      | AR-17-FG-012459-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Iodoform*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 3 reference samples from the substance/substance group *Iodoform*.

| Supplier | Substance | Batch    | Sample ID | Spectra |
|----------|-----------|----------|-----------|---------|
| Caelo    | Iodoform  | 9357608  | 20094     | 40      |
| Caelo    | Iodoform  | 16012302 | 23407     | 40      |
| Caelo    | Iodoform  | 170860   | 23652     | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 180 spectra from 80 *Apo-Ident* customers from 72 batches from the substance/substance group *Iodoform*.

| Supplier | Substance | Batch     | Spectra |
|----------|-----------|-----------|---------|
| Caelo    | Iodoform  | 12283202  | 4       |
| Caelo    | Iodoform  | 12070601  | 5       |
| Caelo    | Iodoform  | 12283206  | 3       |
| fragon   | Iodoform  | 12283303  | 1       |
| Fagron   | Iodoform  | 12E30-N01 | 2       |

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| Supplier                   | Substance | Batch            | Spectra |
|----------------------------|-----------|------------------|---------|
| Fagron                     | Iodoform  | 12L11-B41        | 1       |
| Caelo                      | Iodoform  | 14077601         | 2       |
| Caelo                      | Iodoform  | 14077602         | 1       |
| Caelo                      | Iodoform  | 14077603         | 3       |
| Caelo                      | Iodoform  | 14077606         | 2       |
| Caelo                      | Iodoform  | 14077702         | 7       |
| Caelo                      | Iodoform  | 14230001         | 6       |
| Caelo                      | Iodoform  | 14230002         | 4       |
| Caelo                      | Iodoform  | 14230006         | 3       |
| Caelo                      | Iodoform  | 14230008         | 3       |
| Caelo                      | Iodoform  | 14230007         | 3       |
| Caelo                      | Iodoform  | 14230305         | 5       |
| Caelo                      | Iodoform  | 14230306         | 6       |
| Fagron                     | Iodoform  | 14D09-B14-293029 | 1       |
| Caelo                      | Iodoform  | 15276102         | 2       |
| Caelo                      | Iodoform  | 15276103         | 3       |
| Caelo                      | Iodoform  | 15276105         | 2       |
| Caelo                      | Iodoform  | 15276107         | 1       |
| Caelo                      | Iodoform  | 16012204         | 3       |
| Caelo                      | Iodoform  | 16012305         | 1       |
| Caelo                      | Iodoform  | 1576103          | 1       |
| Caelo                      | Iodoform  | 12070102         | 2       |
| Caelo                      | Iodoform  | 3041407          | 1       |
| Caelo                      | Iodoform  | 10120202         | 1       |
| Anzag ek: 7,28EUR          | Iodoform  | 12070102         | 1       |
| Noweda                     | Iodoform  | 10320402         | 1       |
| Caelo                      | Iodoform  | 12070303         | 2       |
| Caelo                      | Iodoform  | 12070402         | 1       |
| Caelo                      | Iodoform  | 12070407         | 1       |
| Noweda                     | Iodoform  | 12070407         | 1       |
| Caesar & Loretz GmbH, 4... | Iodoform  | 12070501         | 3       |
| Caelo                      | Iodoform  | 12070501         | 1       |
| Kehr                       | Iodoform  | 12070502         | 1       |
| Caelo                      | Iodoform  | 12070502         | 1       |
| Phoenix                    | Iodoform  | 12070601         | 1       |
| Caelo                      | Iodoform  | 12070602         | 3       |
| Caelo                      | Iodoform  | 12070606         | 2       |
| Caelo                      | Iodoform  | 12070605         | 1       |
| Caelo                      | Iodoform  | 12070608         | 5       |
| Caelo                      | Iodoform  | 12150902         | 6       |
| Caelo                      | Iodoform  | 12150903         | 2       |
| Phönix                     | Iodoform  | 12150903         | 1       |
| Caelo                      | Iodoform  | 12150905         | 3       |
| Caelo                      | Iodoform  | 12150907         | 4       |
| Caesar & Loretz GmbH       | Iodoform  | 12150907         | 1       |
| Phoenix                    | Iodoform  | 12150908         | 1       |
| Caelo                      | Iodoform  | 12150908         | 5       |
| Caelo                      | Iodoform  | 12150910         | 5       |
| Caelo                      | Iodoform  | 12283201         | 3       |
| Caelo                      | Iodoform  | 12283303         | 2       |
| Caelo                      | Iodoform  | 12283304         | 2       |
| Caelo                      | Iodoform  | 12283307         | 1       |
| Fagron                     | Iodoform  | 12L11-B41-290055 | 1       |
| Caelo                      | Iodoform  | 14077607         | 1       |
| Euro OTC                   | Iodoform  | 14229504         | 2       |
| Caelo                      | Iodoform  | 14229506         | 1       |
| Caelo                      | Iodoform  | 14229507         | 3       |
| Caelo                      | Iodoform  | 14229508         | 2       |
| Caelo                      | Iodoform  | 14230003         | 1       |
| Caelo                      | Iodoform  | 14230302         | 1       |

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| Supplier | Substance | Batch           | Spectra |
|----------|-----------|-----------------|---------|
| Caelo    | Iodoform  | 14230308        | 5       |
| Caelo    | Iodoform  | 15276002        | 1       |
| Caelo    | Iodoform  | 15276101        | 3       |
| Caelo    | Iodoform  | 15276001        | 3       |
| Caelo    | Iodoform  | 15276104        | 2       |
| Caelo    | Iodoform  | 15276108        | 1       |
| Caelo    | Iodoform  | 15276109        | 1       |
| Caelo    | Iodoform  | 16012201        | 2       |
| Caelo    | Iodoform  | 15276111        | 1       |
| Caelo    | Iodoform  | 16012202        | 1       |
| Caelo    | Iodoform  | 16012206        | 3       |
| Caelo    | Iodoform  | 2013E-01726     | 1       |
| Caelo    | Iodoform  | 21051305        | 1       |
| Kehr     | Iodoform  | 2070602         | 1       |
| Caelo    | Iodoform  | 28011503        | 1       |
| Caelo    | Iodoform  | 12283201/311152 | 1       |

- 69 453 spectra from 414 *Apo-Ident* customers from a total of 23 729 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Iodoform* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Iodoform* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 111           | 9              | 146 609       |
| <b>Type C</b> | 0              | 142           | 38             | 69 453        |

The substance/substance group *Iodoform* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 92.5000 % (> 90.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 78.8889 % (> 77.2222 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.



### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21278     | 23192               | 10.90                        | 89.09                           |
| 21297     | 23192               | 12.00                        | 91.10                           |
| 23192     | 23192               | 0.00                         | 84.94                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ipratropium bromide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20911-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ipratropium bromide; Ipratropii bromidum; Ipratropium bromatum

### Special notes

When selecting the *Ipratropium bromide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ipratropium bromide*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------------|-----------|-----------|---------|-------------|
| Fagron   | Ipratropium brom... | 12C15-N01 | 20911     | 40      | 1403675     |
| Fagron   | Ipratropium brom... | 12K01-N08 | 21272     | 40      | 20121025    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Ipratropium bromide*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *Ipratropium bromide*.

| Supplier | Substance           | Batch            | Sample ID | Spectra |
|----------|---------------------|------------------|-----------|---------|
| Fagron   | Ipratropium bromide | 15C04-B02-321674 | 22747     | 40      |
| Fagron   | Ipratropium bromide | 16K07-B05-335330 | 23597     | 40      |

- 146 649 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Ipratropium bromide*.

| Supplier | Substance           | Batch            | Spectra |
|----------|---------------------|------------------|---------|
| Fagron   | Ipratropium bromide | 14B05-B16-294566 | 1       |

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696

substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ipratropium bromide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ipratropium bromide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 80            | 0              | 71 306        |
| Type B | 0              | 80            | 0              | 146 649       |
| Type C | 0              | 1             | 0              | 69 632        |

The substance/substance group *Ipratropium bromide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| Type C | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20911     | 20911               | 0.00                         | 29.95                           |
| 21272     | 20911               | 8.87                         | 36.15                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Isosorbide dinitrate 40%**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20213-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Isosorbide dinitrate 40%; Isorbidi dinitras 40%; Isosobidum dinatricum 40%

### Special notes

When selecting the *Isosorbide dinitrate 40%* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Isosorbide dinitrate 40%*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Isosorbide dinit... | 12F08-N04        | 20891     | 40      | 20120801    |
| Fagron   | Isosorbide dinit... | 13D15-N02        | 21347     | 39      | 20130410    |
| Fagron   | Isosorbide dinit... | 15I10-B01-328577 | 23200     | 40      | 1709092     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 119 spectra of 3 reference samples from the substance/substance group *Isosorbide dinitrate 40%*. These samples are listed above in the [calibration samples](#) section.
- 71 267 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 110 spectra of 3 reference samples from the substance/substance group *Isosorbide dinitrate 40%*.

| Supplier | Substance                | Batch            | Sample ID | Spectra |
|----------|--------------------------|------------------|-----------|---------|
| Fagron   | Isosorbide dinitrate 40% | 10L09-N10        | 20213     | 40      |
| Fagron   | Isosorbide dinitrate 40% | 15I10-B01-315217 | 22762     | 40      |
| Fagron   | Isosorbide dinitrate 40% | 15I10-B01-328577 | 23598     | 30      |

- 146 619 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 203 spectra from 104 *Apo-Ident* customers from 83 batches from the substance/substance group *Isosorbide dinitrate 40%*.

| Supplier | Substance                | Batch            | Spectra |
|----------|--------------------------|------------------|---------|
| Fagron   | Isosorbide dinitrate 40% | 14D09-B03        | 8       |
| Caelo    | Isosorbide dinitrate 40% | 14D09-B03-294281 | 2       |
| Fagron   | Isosorbide dinitrate 40% | 14D09-B03-300234 | 12      |
| Fagron   | Isosorbide dinitrate 40% | 14D09-B03-307018 | 1       |

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| Supplier                     | Substance                | Batch                | Spectra |
|------------------------------|--------------------------|----------------------|---------|
| Gehe                         | Isosorbide dinitrate 40% | 11D12-N01            | 1       |
| Fagron                       | Isosorbide dinitrate 40% |                      | 2       |
| Caelo                        | Isosorbide dinitrate 40% | 11D12-N01            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 12C08-N05            | 5       |
| Fagron                       | Isosorbide dinitrate 40% | 13D15-N02            | 10      |
| Fagron                       | Isosorbide dinitrate 40% | 12f08-n04            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 13F27-N04            | 9       |
| Fagron                       | Isosorbide dinitrate 40% | 14D09-B03-294280     | 7       |
| VDI 28.10.14 10,32 euro      | Isosorbide dinitrate 40% |                      | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 14D09-B03-29481      | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 14D09-B03-294282     | 3       |
| Fagron                       | Isosorbide dinitrate 40% | 12F08-N04            | 11      |
| Fagron                       | Isosorbide dinitrate 40% | 8564340              | 1       |
| Caelo                        | Isosorbide dinitrate 40% | 11/17-N05            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 11J17-No5            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 101652               | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 10C19-N01            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 11D12-N01            | 4       |
| Fagron                       | Isosorbide dinitrate 40% | 12k14-n02            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 13/26-N18            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 13F27-N040234/1300   | 1       |
| Caelo                        | Isosorbide dinitrate 40% | 13F27-N04            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 13I26-N18            | 9       |
| Fagron                       | Isosorbide dinitrate 40% | 149168               | 2       |
| Sanacorp                     | Isosorbide dinitrate 40% | 14D09-B03-294280     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 14D09-B03294282      | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 14D09-B03-294281     | 4       |
| ebe a                        | Isosorbide dinitrate 40% | 14D09-B03-294281     | 1       |
| AHD 09.03.2015               | Isosorbide dinitrate 40% | 14D09-B03-294281     | 1       |
| Allianz Healthcare 17.0. . . | Isosorbide dinitrate 40% | 14D09-B03-300234     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 14D09-B03-294282Eber | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 14-D09-B03-300234    | 1       |
| Caelo                        | Isosorbide dinitrate 40% | 14D09-B03-307018     | 1       |
| Caelo                        | Isosorbide dinitrate 40% | 14D-09-B03-300234    | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 14D09-B03-308419     | 10      |
| Caelo                        | Isosorbide dinitrate 40% | 14D09-B03-308419     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 14D09-B03-313566     | 1       |
| Wepa                         | Isosorbide dinitrate 40% | 14D09-B03-313566     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 14D09-B3-308419      | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15/10-B01            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15/10-B01-315217     | 3       |
| Noweda                       | Isosorbide dinitrate 40% | 15/10-B01-315217     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15/10-B01-320081     | 1       |
| Fargon                       | Isosorbide dinitrate 40% | 15/10-B01-320081     | 1       |
| Anzag                        | Isosorbide dinitrate 40% | 1510B01315217        | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15/10-B01-325474     | 1       |
| Caelo                        | Isosorbide dinitrate 40% | 1510-B01-315217      | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 1510-B01-320081      | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 1510-B01320081       | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15I10-B01            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15I10-B01-315217     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15I10-B01-310081     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15I10B01320081       | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15I10-B01-320782     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15I10-B01-325474     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15I10-B01-320081     | 2       |
| Ebert-Jacobi                 | Isosorbide dinitrate 40% | 15I10-B01-328132     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 15I10-B01-328577     | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 2114M3516            | 1       |
| Fagron                       | Isosorbide dinitrate 40% | 3115M-03516          | 1       |

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| Supplier                   | Substance                | Batch        | Spectra |
|----------------------------|--------------------------|--------------|---------|
| Fagron                     | Isosorbide dinitrate 40% | 3211U-03516  | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 4314U-03516  | 1       |
| Fagron                     | Isosorbide dinitrate 40% | testxx       | 1       |
| Fagron                     | Isosorbide dinitrate 40% | X12010       | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 9E05-N05     | 2       |
| Fagron                     | Isosorbide dinitrate 40% | 9101205      | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 10029-N10    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 10D29-N10    | 1       |
| Noweda                     | Isosorbide dinitrate 40% | 10G15-N01    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 11/17-N05    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 11/17-No5    | 1       |
| Phönix 22.11.2012          | Isosorbide dinitrate 40% | 11F28-N05    | 1       |
| FARGON                     | Isosorbide dinitrate 40% | 11f20-n05    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 11J17-N05    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 11I17-N05    | 1       |
| Sanacorp                   | Isosorbide dinitrate 40% | 11J17-N05    | 1       |
| Anzag 11.04.12             | Isosorbide dinitrate 40% | 11F28-N05    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 11117-N05    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 1216M-03516  | 1       |
| Fiebig 23.05.13 ek: 10,... | Isosorbide dinitrate 40% | 12F08-N04    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 12K14-N02    | 7       |
| Fagron                     | Isosorbide dinitrate 40% | 12F08N04     | 1       |
| Phönix, 25.09.2013         | Isosorbide dinitrate 40% | 12K14-N02    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 12K14N02     | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 1309210009   | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 13A07-0003   | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 13A07-N13    | 6       |
| Phönix                     | Isosorbide dinitrate 40% | 13A07-N13    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 13d15-n02    | 1       |
| Caelo                      | Isosorbide dinitrate 40% | 13D15-N02    | 3       |
| Fagron                     | Isosorbide dinitrate 40% | 13D15-No2    | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 2405210009   | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 2413Q03516   | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 26061207     | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 3413U03516   | 1       |
| Fagron                     | Isosorbide dinitrate 40% | 391311-03516 | 1       |
| Fagron                     | Isosorbide dinitrate 40% | P11008       | 2       |
| Euro OTC                   | Isosorbide dinitrate 40% |              | 1       |

- 69 430 spectra from 414 *Apo-Ident* customers from a total of 23 718 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Isosorbide dinitrate 40%* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Isosorbide dinitrate 40%* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 119           | 0              | 71 267        |
| Type B | 0              | 110           | 0              | 146 619       |
| Type C | 0              | 189           | 14             | 69 430        |

The substance/substance group *Isosorbide dinitrate* 40% can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.9580 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.5455 %) |
| Type C | 100.0000 % (> 99.8813 %) | 93.1034 % (> 91.6256 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20891     | 23200               | 4.64                         | 39.46                           |
| 21347     | 23200               | 3.51                         | 41.20                           |
| 23200     | 23200               | 0.00                         | 41.23                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Isoxuprine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22640-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Isoxuprine hydrochloride; Isoxuprini hydrochloridum

### Special notes

When selecting the *Isoxuprine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Isoxuprine hydrochloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Caelo    | Isoxuprine hydro... | 161770     | 22640     | 40      | 20160818*   |
| Euro OTC | Isoxuprine hydro... | 1503008-01 | 22659     | 40      | 20150430    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Isoxuprine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 40 spectra of 1 reference samples from the substance/substance group *Isoxuprine hydrochloride*.

| Supplier | Substance                | Batch    | Sample ID | Spectra |
|----------|--------------------------|----------|-----------|---------|
| Caelo    | Isoxuprine hydrochloride | 16177001 | 22735     | 40      |

- 146 689 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Isoxuprine hydrochloride*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

## Validation results

The validation runs checked whether the substance/substance group *Isoxuprine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Isoxuprine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 40            | 0              | 146 689       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Isoxuprine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 85.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22640     | 22640               | 0.00                         | 49.46                           |
| 22659     | 22640               | 6.88                         | 48.91                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ketamine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20278-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ketamine hydrochloride; Ketamini hydrochloridum; Ketaminum hydrochloricum

### Special notes

When selecting the *Ketamine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ketamine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Ketamine hydroch... | 13H19-N01        | 21044     | 40      | 8931        |
| Fagron   | Ketamine hydroch... | 14I03-B02-303165 | 21779     | 40      | 20140926    |
| Fagron   | Ketamine hydroch... | 14I03-B02-311706 | 22533     | 40      | 20140926    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Ketamine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *Ketamine hydrochloride*.

| Supplier | Substance              | Batch            | Sample ID          | Spectra |
|----------|------------------------|------------------|--------------------|---------|
| Fagron   | Ketamine hydrochloride | 11A27-N13        | 20278              | 40      |
| Fagron   | Ketamine hydrochloride | 14I03-B02-303165 | 21779 <sup>†</sup> | 20      |
| Fagron   | Ketamine hydrochloride | 15E07-B03-322164 | 23201              | 40      |

- 146 629 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 14 spectra from 7 *Apo-Ident* customers from 10 batches from the substance/substance group *Ketamine hydrochloride*.

| Supplier | Substance              | Batch   | Spectra |
|----------|------------------------|---------|---------|
| Noweda   | Ketamine hydrochloride | 292414P | 1       |
| Fagron   | Ketamine hydrochloride | 182513P | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

continued from previous page

| Supplier        | Substance              | Batch            | Spectra |
|-----------------|------------------------|------------------|---------|
| GEHE 27.05.2014 | Ketamine hydrochloride | 13H19-N01        | 1       |
| Fagron          | Ketamine hydrochloride | 14/03-B02-303165 | 1       |
| Noweda          | Ketamine hydrochloride | 14/03-B02-311706 | 1       |
| Fagron          | Ketamine hydrochloride | 14I03-B02-309852 | 1       |
| Fagron          | Ketamine hydrochloride | 15E07-B03-322164 | 5       |
| Fagron          | Ketamine hydrochloride | 16E18-B03-328264 | 1       |
| Fagron          | Ketamine hydrochloride | 16E18-B03-332957 | 1       |
| Fagron          | Ketamine hydrochloride | 12F01-N11        | 1       |

- 69 619 spectra from 414 *Apo-Ident* customers from a total of 23 791 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ketamine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ketamine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 60            | 40             | 146 629       |
| <b>Type C</b> | 0              | 8             | 6              | 69 619        |

The substance/substance group *Ketamine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 60.0000 % (> 57.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21044     | 21044               | 0.00                         | 72.55                           |
| 21779     | 21044               | 4.98                         | 72.99                           |
| 22533     | 21044               | 16.39                        | 70.58                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ketoconazole**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20688-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ketoconazole; Ketoconazolum

### Special notes

When selecting the *Ketoconazole* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ketoconazole*:

| Supplier | Substance    | Batch     | Sample ID | Spectra | Certificate |
|----------|--------------|-----------|-----------|---------|-------------|
| Caelo    | Ketoconazole | 12171007  | 20688     | 40      | 1401554     |
| Fagron   | Ketoconazole | 12A16-N06 | 20699     | 40      | 20120123    |
| Caelo    | Ketoconazole | 13179612  | 21514     | 40      | 20130613    |
| Caelo    | Ketoconazole | 13179612  | 21515     | 40      | 20130613    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Ketoconazole*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 4 reference samples from the substance/substance group *Ketoconazole*.

| Supplier | Substance    | Batch            | Sample ID          | Spectra |
|----------|--------------|------------------|--------------------|---------|
| Fagron   | Ketoconazole | 10J18-N07        | 20275              | 40      |
| Caelo    | Ketoconazole | 13179612         | 21514 <sup>†</sup> | 20      |
| Caelo    | Ketoconazole | 13179612         | 21515 <sup>†</sup> | 20      |
| Fagron   | Ketoconazole | 16A26-B01-322982 | 23183              | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 56 spectra from 34 *Apo-Ident* customers from 32 batches from the substance/substance group *Ketoconazole*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier          | Substance    | Batch            | Spectra |
|-------------------|--------------|------------------|---------|
| Caelo             | Ketoconazole | 12300407         | 4       |
| Caelo             | Ketoconazole | 12300415         | 1       |
| Caelo             | Ketoconazole | 13179606         | 3       |
| Caelo             | Ketoconazole | 13179610         | 4       |
| Fagron            | Ketoconazole | 13179612         | 1       |
| Caelo             | Ketoconazole | 13179612         | 1       |
| Caelo             | Ketoconazole | 13399404         | 7       |
| Caelo             | Ketoconazole | 13399408         | 4       |
| Fagron            | Ketoconazole | 13H09-N07        | 1       |
| Caelo             | Ketoconazole | 14350408         | 1       |
| Fagron            | Ketoconazole | 13J23-N04        | 1       |
| ANZAG 23.07.14    | Ketoconazole | 13h09-n07        | 1       |
| Caelo             | Ketoconazole | 14350422         | 1       |
| Fagron            | Ketoconazole | 14K04-B06-309671 | 1       |
| Caelo             | Ketoconazole | 14350419         | 1       |
| Caelo             | Ketoconazole | 14350429         | 1       |
| Caelo             | Ketoconazole | 14350436         | 1       |
| Fagron            | Ketoconazole | 14E09-B01-293736 | 2       |
| Fagron            | Ketoconazole | 15G23-B03-312063 | 1       |
| Caelo             | Ketoconazole | 53317046         | 2       |
| Gehe              | Ketoconazole | 11070019         | 1       |
| Caelo             | Ketoconazole | 11070001         | 1       |
| Caelo             | Ketoconazole | 11070022         | 2       |
| Caelo             | Ketoconazole | 12171007         | 1       |
| anzag, 14.11.2012 | Ketoconazole | 12171008         | 1       |
| Caelo             | Ketoconazole | 12171008         | 1       |
| Phönix            | Ketoconazole | 12171018         | 1       |
| Caelo             | Ketoconazole | 12300406         | 1       |
| Fagron            | Ketoconazole | 12I17-N02        | 1       |
| Fagron            | Ketoconazole | 12I17-N02        | 1       |
| Caelo             | Ketoconazole | 13179601         | 1       |
| Phönix            | Ketoconazole | 13179602         | 3       |
| Fagron            | Ketoconazole | 14E09-B01-297637 | 1       |
| Fagron            | Ketoconazole | 5015E-02866      | 1       |

- 69 577 spectra from 414 *Apo-Ident* customers from a total of 23 769 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ketoconazole* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ketoconazole* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 110           | 10             | 146 609       |
| <b>Type C</b> | 0              | 55            | 1              | 69 577        |

The substance/substance group *Ketoconazole* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| Type B | 100.0000 % (> 99.9923 %) | 91.6667 % (> 89.1667 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 98.2143 % (> 92.8571 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20688     | 20688               | 0.00                         | 89.37                           |
| 20699     | 20688               | 8.31                         | 91.42                           |
| 21514     | 20688               | 4.59                         | 91.52                           |
| 21515     | 20688               | 4.79                         | 91.36                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Lactose monohydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20029-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Lactose monohydrate; Lactosum monohydricum; Saccharum lactis

### Special notes

When selecting the *Lactose monohydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Lactose monohydrate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Lactose monohydr... | 12139910 | 20685     | 40      | 20120606    |
| Caelo    | Lactose monohydr... | 14025601 | 21525     | 40      | 20140207    |
| Euro OTC | Lactose monohydr... | 1509030  | 21935     | 40      | 20151013*   |
| Caelo    | Lactose monohydr... | 160277   | 22460     | 40      | 20160321*   |
| Euro OTC | Lactose monohydr... | 1606025  | 22701     | 40      | 20160628*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Lactose monohydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 310 spectra of 9 reference samples from the substance/substance group *Lactose monohydrate*.

| Supplier | Substance           | Batch    | Sample ID          | Spectra |
|----------|---------------------|----------|--------------------|---------|
| Caelo    | Lactose monohydrate | 83278189 | 20029              | 30      |
| Caelo    | Lactose monohydrate | 14025601 | 21526              | 40      |
| Caelo    | Lactose monohydrate | 14025601 | 21527              | 40      |
| Caelo    | Lactose monohydrate | 14025601 | 21528              | 40      |
| Caelo    | Lactose monohydrate | 14025601 | 21529              | 40      |
| Euro OTC | Lactose monohydrate | 1509030  | 21935 <sup>†</sup> | 20      |
| Caelo    | Lactose monohydrate | 160277   | 22460 <sup>†</sup> | 20      |
| Caelo    | Lactose monohydrate | 15236220 | 22584              | 40      |
| Euro OTC | Lactose monohydrate | 1703019  | 23141              | 40      |

- 146 419 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 708 spectra from 173 *Apo-Ident* customers from 264 batches from the substance/substance group *Lactose monohydrate*.

| Supplier           | Substance           | Batch            | Spectra |
|--------------------|---------------------|------------------|---------|
| Caelo              | Lactose monohydrate | 3031501          | 1       |
| Caelo              | Lactose monohydrate | 3091405          | 1       |
| Caelo              | Lactose monohydrate | 3121406          | 1       |
| Eigenherstellung   | Lactose monohydrate | 40815HMS01       | 1       |
| Caelo              | Lactose monohydrate | 5061504          | 1       |
| Eigenherstellung   | Lactose monohydrate | 60814HSA01       | 1       |
| Caelo              | Lactose monohydrate | 7031402          | 1       |
| Caelo              | Lactose monohydrate | 7111402          | 1       |
| Caelo              | Lactose monohydrate | 9051401          | 1       |
| Caelo              | Lactose monohydrate | 8071501          | 1       |
| Fagron             | Lactose monohydrate | 10751120         | 1       |
| Caelo              | Lactose monohydrate | 10195107         | 3       |
| Anzag/Fragon       | Lactose monohydrate | 1005SLP          | 1       |
| Caelo              | Lactose monohydrate | 12041401         | 1       |
| Caelo              | Lactose monohydrate | 123Test          | 1       |
| Caelo              | Lactose monohydrate | 12399107         | 1       |
| Caelo              | Lactose monohydrate | 123test          | 1       |
| Fagron             | Lactose monohydrate | 13/23-B03-291114 | 1       |
| Euro OTC           | Lactose monohydrate | 1301028-01       | 9       |
| Phönix/Euro        | Lactose monohydrate | 1301028-02       | 2       |
| Euro OTC           | Lactose monohydrate | 1301028-02       | 13      |
| Gehe               | Lactose monohydrate | 1301028-02       | 1       |
| Caelo              | Lactose monohydrate | 1301028-02       | 4       |
| Caelo              | Lactose monohydrate | 13104901         | 7       |
| Caelo              | Lactose monohydrate | 13104909         | 5       |
| Phoenix 19.03.2014 | Lactose monohydrate | 13104909         | 1       |
| Caelo              | Lactose monohydrate | 13104910         | 3       |
| Caelo              | Lactose monohydrate | 13104911         | 3       |
| Caelo              | Lactose monohydrate | 13299101         | 11      |
| Caelo              | Lactose monohydrate | 13299102         | 13      |
| Caelo              | Lactose monohydrate | 13299103         | 2       |
| Caelo              | Lactose monohydrate | 13299106         | 2       |
| Caelo              | Lactose monohydrate | 13299107         | 6       |
| Caelo              | Lactose monohydrate | 13299108         | 5       |
| Sanacorp           | Lactose monohydrate | 13299108         | 1       |
| GEHE am 17.06.2014 | Lactose monohydrate | 13299108         | 1       |
| Caelo              | Lactose monohydrate | 13299112         | 1       |
| Fagron             | Lactose monohydrate | 13E23-B01-283332 | 4       |
| Fagron             | Lactose monohydrate | 13I23-B03        | 4       |
| Fagron             | Lactose monohydrate | 13I23-B03-287414 | 1       |
| AHD                | Lactose monohydrate | 13I23-B03-291114 | 1       |
| Fagron             | Lactose monohydrate | 13I23-B03-291115 | 1       |
| Fagron             | Lactose monohydrate | 13I23-B03-291116 | 1       |
| Fagron             | Lactose monohydrate | 13J23-B03-291114 | 1       |
| Euro OTC           | Lactose monohydrate | 1401003-01       | 13      |
| gehe               | Lactose monohydrate | 1401003-01       | 2       |
| Caelo              | Lactose monohydrate | 1401003-01       | 1       |
| EuRho/Phönix       | Lactose monohydrate | 1401003-01       | 2       |
| EuRho              | Lactose monohydrate | 1401003-01       | 3       |
| Euro OTC           | Lactose monohydrate | 1401003-02       | 4       |
| Euroo/Phoenix      | Lactose monohydrate | 1401003-02       | 1       |
| Euro/Phönix        | Lactose monohydrate | 1401003-02       | 1       |

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| <b>Supplier</b>  | <b>Substance</b>    | <b>Batch</b>     | <b>Spectra</b> |
|------------------|---------------------|------------------|----------------|
| Europ Ots Pharma | Lactose monohydrate | 1401003-02       | 1              |
| Bahnhof-Apotheke | Lactose monohydrate | 140220           | 1              |
| Caelo            | Lactose monohydrate | 1402504          | 1              |
| Caelo            | Lactose monohydrate | 14025601         | 3              |
| Noweda           | Lactose monohydrate | 14025601         | 1              |
| Caelo            | Lactose monohydrate | 14025603         | 7              |
| Caelo            | Lactose monohydrate | 14025604         | 9              |
| Caelo            | Lactose monohydrate | 14025608         | 2              |
| Caelo            | Lactose monohydrate | 14025615         | 1              |
| Caelo            | Lactose monohydrate | 14025616         | 4              |
| Caelo            | Lactose monohydrate | 14025611         | 1              |
| Phönix           | Lactose monohydrate | 14025616         | 1              |
| Caelo            | Lactose monohydrate | 14025619         | 4              |
| Caelo            | Lactose monohydrate | 14025620         | 8              |
| Sanacorp         | Lactose monohydrate | 14025620         | 1              |
| Caesar u. Loretz | Lactose monohydrate | 14025620         | 1              |
| Schubert/Phoenix | Lactose monohydrate | 1404PLV-1928     | 4              |
| Caelo            | Lactose monohydrate | 14140302         | 4              |
| Caelo            | Lactose monohydrate | 14140304         | 4              |
| Caelo            | Lactose monohydrate | 14140305         | 7              |
| Gehe             | Lactose monohydrate | 14140306         | 1              |
| Caelo            | Lactose monohydrate | 14140306         | 2              |
| Caelo            | Lactose monohydrate | 14140308         | 6              |
| Caelo            | Lactose monohydrate | 14140309         | 2              |
| Caelo            | Lactose monohydrate | 14140312         | 11             |
| Caelo            | Lactose monohydrate | 14333501         | 4              |
| Caelo            | Lactose monohydrate | 14333502         | 1              |
| Caelo            | Lactose monohydrate | 14333503         | 1              |
| Caelo            | Lactose monohydrate | 14333508         | 1              |
| Caelo            | Lactose monohydrate | 14333509         | 6              |
| Sanacorp         | Lactose monohydrate | 14333509         | 1              |
| Caelo            | Lactose monohydrate | 14333510         | 1              |
| Caelo            | Lactose monohydrate | 14333511         | 3              |
| Caelo            | Lactose monohydrate | 143335114        | 1              |
| Caelo            | Lactose monohydrate | 14333513         | 3              |
| Caelo            | Lactose monohydrate | 14333518         | 3              |
| Sanacorp         | Lactose monohydrate | 14333518         | 1              |
| Fagron           | Lactose monohydrate | 14333518         | 1              |
| Caelo            | Lactose monohydrate | 14333520         | 7              |
| Caelo            | Lactose monohydrate | 14333521         | 4              |
| Fagron           | Lactose monohydrate | 14333525         | 1              |
| Caelo            | Lactose monohydrate | 14333528         | 2              |
| Caelo            | Lactose monohydrate | 1433502          | 1              |
| Caelo            | Lactose monohydrate | 1433510          | 1              |
| Caelo            | Lactose monohydrate | 1433520          | 1              |
| Caesar u Loretz  | Lactose monohydrate | 1433520          | 1              |
| Caelo            | Lactose monohydrate | 14335313         | 1              |
| Fagron           | Lactose monohydrate | 14A30-B07        | 2              |
| Fagron           | Lactose monohydrate | 14H27-B01-305666 | 1              |
| Fagron           | Lactose monohydrate | 14H27-B02        | 1              |
| Euro OTC         | Lactose monohydrate | 15010            | 1              |
| Caelo            | Lactose monohydrate | 1501017-01       | 4              |
| Euro OTC         | Lactose monohydrate | 1501017-01       | 10             |
| Euro OTC         | Lactose monohydrate | 150101701        | 1              |
| Euro OTC         | Lactose monohydrate | 1501017-02       | 1              |
| Caelo            | Lactose monohydrate | 15011701         | 1              |
| Euro OTC         | Lactose monohydrate | 1509030-01       | 5              |
| Rondell Apotheke | Lactose monohydrate | 1509030-01       | 2              |
| Caelo            | Lactose monohydrate | 150903002        | 1              |
| Euro OTC         | Lactose monohydrate | 15090-30-02      | 1              |

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| <b>Supplier</b>         | <b>Substance</b>    | <b>Batch</b>     | <b>Spectra</b> |
|-------------------------|---------------------|------------------|----------------|
| Euro OTC                | Lactose monohydrate | 150903002        | 1              |
| EuRho                   | Lactose monohydrate | 1509030-02       | 1              |
| Caelo                   | Lactose monohydrate | 15236201         | 13             |
| Caelo                   | Lactose monohydrate | 15236202         | 1              |
| Caelo                   | Lactose monohydrate | 15236204         | 6              |
| Caesar & Loretz/Noweda  | Lactose monohydrate | 15236204         | 1              |
| Caelo                   | Lactose monohydrate | 15236206         | 1              |
| Caelo                   | Lactose monohydrate | 15236208         | 8              |
| Caelo                   | Lactose monohydrate | 15236209         | 4              |
| Caelo                   | Lactose monohydrate | 15236214         | 5              |
| Caelo                   | Lactose monohydrate | 15236215         | 3              |
| Ebert u. Jacobi 18.0... | Lactose monohydrate | 15236215         | 1              |
| Caelo                   | Lactose monohydrate | 15236217         | 1              |
| Caelo                   | Lactose monohydrate | 15236220         | 4              |
| Caelo                   | Lactose monohydrate | 15236221         | 5              |
| Caelo                   | Lactose monohydrate | 1526201          | 1              |
| Fagron                  | Lactose monohydrate | 15A19-B06        | 2              |
| Phoenix                 | Lactose monohydrate | 15A19-B06        | 3              |
| Fagron                  | Lactose monohydrate | 15A19-B06-303437 | 3              |
| Fagron                  | Lactose monohydrate | 15A19-B06-303439 | 1              |
| Fagron                  | Lactose monohydrate | 15H14-B03-314451 | 3              |
| Caelo                   | Lactose monohydrate | 16027701         | 2              |
| Caelo                   | Lactose monohydrate | 16027702         | 1              |
| Caelo                   | Lactose monohydrate | 16027703         | 2              |
| Caelo                   | Lactose monohydrate | 16027704         | 1              |
| Caelo                   | Lactose monohydrate | 16027706         | 1              |
| Caelo                   | Lactose monohydrate | 16027707         | 1              |
| Alte Apotheke           | Lactose monohydrate | 16027708         | 1              |
| Caelo                   | Lactose monohydrate | 16027708         | 2              |
| Euro OTC                | Lactose monohydrate | 1606025-01       | 4              |
| Euro OTC                | Lactose monohydrate | 160602501        | 1              |
| Euro OTC                | Lactose monohydrate | 1606025-02       | 2              |
| Caelo                   | Lactose monohydrate | 16231202         | 6              |
| Caelo                   | Lactose monohydrate | 16231201         | 1              |
| Caesar u Loretz         | Lactose monohydrate | 16231202         | 1              |
| Caelo                   | Lactose monohydrate | 16231203         | 1              |
| Caelo                   | Lactose monohydrate | 16231207         | 2              |
| Caelo                   | Lactose monohydrate | 16231208         | 2              |
| Caelo                   | Lactose monohydrate | 16231211         | 3              |
| Gehe                    | Lactose monohydrate | 16231211         | 1              |
| Caelo                   | Lactose monohydrate | 16231214         | 2              |
| Euro OTC                | Lactose monohydrate | 18082014A        | 1              |
| Caelo                   | Lactose monohydrate | 200415HJK02      | 1              |
| Caelo                   | Lactose monohydrate | 23051501         | 1              |
| Caelo                   | Lactose monohydrate | 23061504         | 1              |
| Caelo                   | Lactose monohydrate | 23101404         | 1              |
| Bombastus               | Lactose monohydrate | 291464           | 1              |
| Caelo                   | Lactose monohydrate | 26071401         | 1              |
| Bombastus               | Lactose monohydrate | 293918/0         | 1              |
| Bombastus               | Lactose monohydrate | 294184/0         | 1              |
| Bombastus               | Lactose monohydrate | 294897/0         | 1              |
| Bombastus               | Lactose monohydrate | 295011/0         | 1              |
| Caelo                   | Lactose monohydrate | 30031503         | 1              |
| Euro OTC                | Lactose monohydrate | 3215A-02210      | 1              |
| Euro OTC                | Lactose monohydrate | 5123             | 1              |
| Gatt-Koller             | Lactose monohydrate | 5580/12120813    | 2              |
| Caelo                   | Lactose monohydrate | 1071302          | 1              |
| Eigenherstellung        | Lactose monohydrate | 30912HML01       | 1              |
| Eigenherstellung        | Lactose monohydrate | 40113HJK01       | 1              |
| Caelo                   | Lactose monohydrate | 6091301          | 1              |

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| Supplier                 | Substance           | Batch            | Spectra |
|--------------------------|---------------------|------------------|---------|
| Eigenherstellung         | Lactose monohydrate | 70113HML01       | 1       |
| Caelo                    | Lactose monohydrate | 8021401          | 1       |
| Alliance Healthcare      | Lactose monohydrate | 10195101         | 1       |
| Caelo                    | Lactose monohydrate | 11014714         | 1       |
| Europharm/Otto           | Lactose monohydrate | 1106022-01       | 1       |
| Gehe                     | Lactose monohydrate | 1106022-02       | 2       |
| Caelo                    | Lactose monohydrate | 1106022-02       | 1       |
| Noweda                   | Lactose monohydrate | 1106022-02       | 1       |
| Euro OTC                 | Lactose monohydrate | 110602202        | 1       |
| Caelo                    | Lactose monohydrate | 11079002         | 2       |
| Eigenherstellung         | Lactose monohydrate | 110913HJK01      | 1       |
| Euro OTC                 | Lactose monohydrate | 1112020-01       | 3       |
| EuRho                    | Lactose monohydrate | 1112020-01       | 1       |
| vdl                      | Lactose monohydrate | 1112020-01       | 2       |
| Gehe                     | Lactose monohydrate | 1112020-01       | 2       |
| Gehe                     | Lactose monohydrate | 1112020-02       | 7       |
| Euro OTC                 | Lactose monohydrate | 1112020-02       | 5       |
| Gehe                     | Lactose monohydrate | 11120220-01      | 1       |
| Caelo                    | Lactose monohydrate | 11219208         | 3       |
| Caelo                    | Lactose monohydrate | 11219216         | 4       |
| Fagron                   | Lactose monohydrate | 12/23-B02-287554 | 1       |
| Fagron                   | Lactose monohydrate | 11C29-N06        | 1       |
| Fagron                   | Lactose monohydrate | 11L22-N03        | 1       |
| Caelo                    | Lactose monohydrate | 12021502         | 2       |
| Caelo                    | Lactose monohydrate | 12021507         | 3       |
| Caelo                    | Lactose monohydrate | 12021508         | 2       |
| GEHE                     | Lactose monohydrate | 12021508         | 1       |
| Caelo                    | Lactose monohydrate | 12021518         | 12      |
| Bahnhof-Apotheke         | Lactose monohydrate | 120614           | 1       |
| Bahnhof-Apotheke Kempten | Lactose monohydrate | 120808           | 1       |
| Bahnhof-Apotheke         | Lactose monohydrate | 120808           | 1       |
| Bahnhof-Apotheke         | Lactose monohydrate | 121119           | 2       |
| Caelo                    | Lactose monohydrate | 12139901         | 4       |
| Caelo                    | Lactose monohydrate | 12139909         | 1       |
| Caelo                    | Lactose monohydrate | 12139910         | 3       |
| Herbasinica              | Lactose monohydrate | 12139910         | 1       |
| Caelo                    | Lactose monohydrate | 12139914         | 6       |
| Anzag 29.11.12 ek:7,51   | Lactose monohydrate | 12139914         | 1       |
| Caelo                    | Lactose monohydrate | 12139915         | 4       |
| Anzag                    | Lactose monohydrate | 12139915         | 5       |
| Caelo                    | Lactose monohydrate | 12139920         | 6       |
| Caelo                    | Lactose monohydrate | 12336801         | 6       |
| Caelo                    | Lactose monohydrate | 12336803         | 1       |
| Caelo                    | Lactose monohydrate | 12336804         | 1       |
| Caelo                    | Lactose monohydrate | 12336814         | 1       |
| Caelo                    | Lactose monohydrate | 12336815         | 11      |
| Noweda/ Caesar&Loretz    | Lactose monohydrate | 12336815         | 1       |
| Anzag 11.06.2013         | Lactose monohydrate | 12336815         | 1       |
| Sanacorp                 | Lactose monohydrate | 12336815         | 1       |
| Phönix                   | Lactose monohydrate | 12336815         | 1       |
| cesar&llorentz/Phönix    | Lactose monohydrate | 12336815         | 1       |
| Caelo                    | Lactose monohydrate | 12336816         | 5       |
| Caelo                    | Lactose monohydrate | 12336820         | 4       |
| Caelo                    | Lactose monohydrate | 12336821         | 1       |
| Fagron                   | Lactose monohydrate | 12C09-N04        | 1       |
| Fagron                   | Lactose monohydrate | 12G27-N02        | 5       |
| Fagron                   | Lactose monohydrate | 12C26-N05        | 1       |
| Fagron                   | Lactose monohydrate | 13/23-B02-287554 | 1       |
| Euro OTC                 | Lactose monohydrate | 130102801        | 1       |
| EuRho                    | Lactose monohydrate | 1301028-01       | 1       |

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| <b>Supplier</b>    | <b>Substance</b>    | <b>Batch</b>     | <b>Spectra</b> |
|--------------------|---------------------|------------------|----------------|
| Sanacorp           | Lactose monohydrate | 1301028-01       | 1              |
| Bahnhof-Apotheke   | Lactose monohydrate | 130115           | 1              |
| Fagron             | Lactose monohydrate | 1301C005         | 2              |
| Fagron             | Lactose monohydrate | 1301C005-278129  | 2              |
| Fagron             | Lactose monohydrate | 1301C006-278128  | 4              |
| Caelo              | Lactose monohydrate | 1301C006-278128  | 1              |
| Fagron             | Lactose monohydrate | 1301C007-278131  | 1              |
| Fagron             | Lactose monohydrate | 1303C001         | 1              |
| Fagron             | Lactose monohydrate | 1301C008-278130  | 1              |
| Fagron             | Lactose monohydrate | 1303C001-280388  | 2              |
| Fagron             | Lactose monohydrate | 1303C002-280398  | 1              |
| Fagron             | Lactose monohydrate | 1303C003         | 1              |
| Fagron             | Lactose monohydrate | 1303C003-280390  | 1              |
| Bahnhof-Apotheke   | Lactose monohydrate | 130729           | 1              |
| Caelo              | Lactose monohydrate | 13081302         | 1              |
| Fagron             | Lactose monohydrate | 13088R           | 1              |
| Bahnhof-Apotheke   | Lactose monohydrate | 130911           | 1              |
| Bahnhof-Apotheke   | Lactose monohydrate | 130925           | 1              |
| Fagron             | Lactose monohydrate | 13096R           | 1              |
| Cealo              | Lactose monohydrate | 13104901         | 1              |
| gehe 12.09.13      | Lactose monohydrate | 13104901         | 1              |
| Caelo              | Lactose monohydrate | 13104902         | 8              |
| Caelo              | Lactose monohydrate | 13104908         | 3              |
| Phönix             | Lactose monohydrate | 13299102         | 2              |
| Sanacorp           | Lactose monohydrate | 13299102         | 1              |
| schubert / Phoenix | Lactose monohydrate | 1334PLV-1775     | 1              |
| Fagron             | Lactose monohydrate | 13E23-B01        | 2              |
| Fagron             | Lactose monohydrate | 13E23-B01-283334 | 2              |
| Euro OTC           | Lactose monohydrate | 140-1003-01      | 1              |
| Bahnhof-Apotheke   | Lactose monohydrate | 140113           | 3              |
| Caelo              | Lactose monohydrate | 160913PK01       | 1              |
| Caelo              | Lactose monohydrate | 17011302         | 1              |
| Caelo              | Lactose monohydrate | 17011301         | 1              |
| Caelo              | Lactose monohydrate | 20021411         | 1              |
| Caelo              | Lactose monohydrate | 24011405         | 1              |
| Caelo              | Lactose monohydrate | 25011303         | 1              |
| Bombastus          | Lactose monohydrate | 272680/0         | 1              |
| Bombastus          | Lactose monohydrate | 275194/0         | 1              |
| Bombastus          | Lactose monohydrate | 274926           | 1              |
| Bombastus          | Lactose monohydrate | 275225/0         | 1              |
| Fagron             | Lactose monohydrate | 282567/0         | 1              |
| Bombastus          | Lactose monohydrate | 282648           | 1              |
| Bombastus          | Lactose monohydrate | 282696/0         | 1              |
| Bombastus          | Lactose monohydrate | 283992           | 2              |
| Bombastus          | Lactose monohydrate | 284321/0         | 1              |
| Bombastus          | Lactose monohydrate | 285087/0         | 1              |
| Bombastus          | Lactose monohydrate | 286697/0         | 1              |
| Bombastus          | Lactose monohydrate | 288015/0         | 1              |
| Bombastus          | Lactose monohydrate | 288927           | 1              |
| Bombastus          | Lactose monohydrate | 289238           | 1              |
| Caelo              | Lactose monohydrate | 2901312210       | 1              |
| Caelo              | Lactose monohydrate | 30101201         | 1              |
| Caelo              | Lactose monohydrate | 31081301         | 1              |
| Euro OTC           | Lactose monohydrate | 31102013A        | 1              |
| Caelo              | Lactose monohydrate | 4313Q2210        | 1              |
| Caelo              | Lactose monohydrate | 3788916          | 1              |
| Caelo              | Lactose monohydrate | 6859858          | 1              |
| Spangropharm       | Lactose monohydrate | 91444379         | 1              |
| Euro OTC           | Lactose monohydrate | L1237A4172       | 1              |
| Caelo              | Lactose monohydrate | s-100513-1       | 1              |

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| Supplier                   | Substance           | Batch               | Spectra |
|----------------------------|---------------------|---------------------|---------|
| Bahnhof-Apotheke           | Lactose monohydrate | 140206              | 2       |
| Bahnhof-Apotheke           | Lactose monohydrate | 140310              | 2       |
| Caelo                      | Lactose monohydrate | 140612              | 3       |
| Caelo/Noweda               | Lactose monohydrate | 1523204             | 1       |
| Sanacorp,05.04.17, 5,96EUR | Lactose monohydrate | 16231202            | 1       |
| Noweda                     | Lactose monohydrate | 1112020-01          | 1       |
| Caelo                      | Lactose monohydrate | 11219217            | 1       |
| Fagron                     | Lactose monohydrate | 11H04-N04           | 1       |
| Caelo                      | Lactose monohydrate | 120403              | 1       |
| Caelo                      | Lactose monohydrate | 12139908            | 2       |
| Caelo                      | Lactose monohydrate | 12139912            | 2       |
| Fagron                     | Lactose monohydrate | 1301C006            | 1       |
| Bahnhof-Apotheke           | Lactose monohydrate | 131112              | 1       |
| Bahnhof-Apotheke           | Lactose monohydrate | 131127              | 2       |
| Bahnhof-Apotheke           | Lactose monohydrate | 131218              | 2       |
| Fagron                     | Lactose monohydrate | 10726158            | 1       |
| Euro OTC                   | Lactose monohydrate | 1013Q-02210         | 1       |
| Fagron                     | Lactose monohydrate | 14A30-B07-296182    | 2       |
| Nachprüfung                | Lactose monohydrate | 3712Q-02210         | 1       |
| Anzag / Noweda             | Lactose monohydrate | 12336815            | 1       |
| Peter Kölln                | Lactose monohydrate | 229719241-0640      | 1       |
| Caelo                      | Lactose monohydrate |                     | 1       |
| Bahnhofsapotheke           | Lactose monohydrate | 140401              | 1       |
| Bahnhof-Apotheke           | Lactose monohydrate | 140630              | 1       |
| Fragon                     | Lactose monohydrate | 10706040            | 1       |
|                            | Lactose monohydrate | 12021518            | 1       |
| A.H.D.                     | Lactose monohydrate | 12336801            | 1       |
| Bahnhof-Apotheke           | Lactose monohydrate | 131023              | 1       |
| Sanacorp                   | Lactose monohydrate | 13104901            | 1       |
| Caelo                      | Lactose monohydrate | 13104909-3453311172 | 1       |
| Caelo                      | Lactose monohydrate | 13104909-3422310182 | 1       |
| Caelo                      | Lactose monohydrate | 13104912            | 2       |
| Sanacorp                   | Lactose monohydrate | 13104909            | 1       |

- 68 925 spectra from 414 *Apo-Ident* customers from a total of 23 545 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Lactose monohydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Lactose monohydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 310           | 0              | 146 419       |
| <b>Type C</b> | 0              | 705           | 3              | 68 925        |

The substance/substance group *Lactose monohydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:



|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.0645 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 99.5763 % (> 99.1525 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 20685            | 22701                      | 2.10                                | 42.76                                  |
| 21525            | 21935                      | 3.57                                | 41.02                                  |
| 21935            | 21935                      | 0.00                                | 41.80                                  |
| 22460            | 22460                      | 0.00                                | 42.56                                  |
| 22701            | 22701                      | 0.00                                | 42.38                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Levocarnitine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20357-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Levocarnitine; Levocarnitivum

### Special notes

When selecting the *Levocarnitine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Levocarnitine*:

| Supplier | Substance     | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------|------------------|-----------|---------|--------------------|
| Euro OTC | Levocarnitine | 1210029-01       | 20809     | 40      | 20121130           |
| Fagron   | Levocarnitine | 12H10-N07        | 20818     | 40      | 20120830           |
| Fagron   | Levocarnitine | 14A20-B11-290728 | 21790     | 40      | AR-15-FG-016322-01 |
| Fagron   | Levocarnitine | 14A20-B11-290728 | 21968     | 40      | AR-16-FG-005969-01 |
| Fagron   | Levocarnitine | 15L04-B05-319229 | 23194     | 40      | AR-17-FG-012937-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Levocarnitine*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 225 spectra of 6 reference samples from the substance/substance group *Levocarnitine*.

| Supplier | Substance     | Batch            | Sample ID          | Spectra |
|----------|---------------|------------------|--------------------|---------|
| Fagron   | Levocarnitine | 11E18-N06        | 20285              | 45      |
| Euro OTC | Levocarnitine | 1106012-02       | 20357              | 40      |
| Euro OTC | Levocarnitine | 1303027-02       | 21648              | 60      |
| Fagron   | Levocarnitine | 14A20-B11-290728 | 21790 <sup>†</sup> | 20      |
| Fagron   | Levocarnitine | 14A20-B11-290728 | 21968 <sup>†</sup> | 20      |
| Fagron   | Levocarnitine | 16F20-B01-326616 | 23402              | 40      |

- 146 504 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 10 spectra from 6 *Apo-Ident* customers from 8 batches from the substance/substance group *Levocarnitine*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance     | Batch       | Spectra |
|----------|---------------|-------------|---------|
| Fagron   | Levocarnitine | 13G19-N12   | 3       |
| Fagron   | Levocarnitine | 9041504     | 1       |
| Fagron   | Levocarnitine | 130526      | 1       |
| Euro OTC | Levocarnitine | 1106012-020 | 1       |
| Fagron   | Levocarnitine | 150104      | 1       |
| Euro OTC | Levocarnitine | 1303027     | 1       |
| Euro OTC | Levocarnitine | 7120        | 1       |
| Euro OTC | Levocarnitine | 1303027-01  | 1       |

- 69 623 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Levocarnitine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Levocarnitine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 180           | 45             | 146 504       |
| <b>Type C</b> | 0              | 9             | 1              | 69 623        |

The substance/substance group *Levocarnitine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 80.0000 % (> 78.6667 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20809     | 23194               | 14.05                        | 28.89                           |
| 20818     | 23194               | 20.13                        | 32.84                           |
| 21790     | 21790               | 0.00                         | 44.65                           |
| 21968     | 21968               | 0.00                         | 76.20                           |
| 23194     | 23194               | 0.00                         | 38.41                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Levothyroxine sodium**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21708-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Levothyroxine sodium; Levothyroxinum natrii

### Special notes

When selecting the *Levothyroxine sodium* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Levothyroxine sodium*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Levothyroxine so... | 14E28-B05-298322 | 21708     | 20      | 1506426     |
| Fagron   | Levothyroxine so... | 14E28-B05-306102 | 21820     | 40      | 20140915    |
| Fagron   | Levothyroxine so... | 14E28-B05-298322 | 21708SI   | 32      | 1506426     |
| Fagron   | Levothyroxine so... | 14E28-B05-306102 | 21820SI   | 38      | 20140915    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 130 spectra of 4 reference samples from the substance/substance group *Levothyroxine sodium*. These samples are listed above in the [calibration samples](#) section.
- 71 256 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 141 spectra of 7 reference samples from the substance/substance group *Levothyroxine sodium*.

| Supplier | Substance            | Batch            | Sample ID            | Spectra |
|----------|----------------------|------------------|----------------------|---------|
| Fagron   | Levothyroxine sodium | 14E28-B05-298322 | 21708 <sup>†</sup>   | 10      |
| Fagron   | Levothyroxine sodium | 14E28-B05-306102 | 21820 <sup>†</sup>   | 20      |
| Fagron   | Levothyroxine sodium | 16G25-B99-329080 | 23191                | 40      |
| Fagron   | Levothyroxine sodium | 16G25-B99-324827 | not required         | 17      |
| Fagron   | Levothyroxine sodium | 14E28-B05-298322 | 21708SI <sup>†</sup> | 15      |
| Fagron   | Levothyroxine sodium | 14E28-B05-306102 | 21820SI <sup>†</sup> | 15      |
| Fagron   | Levothyroxine sodium | 16G25-B99-329080 | 23191SI              | 24      |

- 146 588 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Levothyroxine sodium*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Levothyroxine sodium* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Levothyroxine sodium* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 124           | 6              | 71 256        |
| <b>Type B</b> | 0              | 128           | 13             | 146 588       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Levothyroxine sodium* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate        |
|---------------|--------------------------|-------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 95.3846 % (> 93.0769 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 90.7801 % (> 88.6525 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)               |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21708     | 21708               | 0.00                         | 74.01                           |
| 21820     | 21708               | 19.61                        | 82.96                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe

von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **L-glutathione**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20366-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

L-glutathione; L-Glutathionum

### Special notes

When selecting the *L-glutathione* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *L-glutathione*:

| Supplier | Substance     | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------|------------|-----------|---------|--------------------|
| Euro OTC | L-glutathione | 1102019-02 | 21788     | 40      | AR-15-FG-008218-01 |
| Euro OTC | L-glutathione | 1703008    | 23143     | 40      | 20170327*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group L-glutathione. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group L-glutathione.

| Supplier | Substance     | Batch       | Sample ID          | Spectra |
|----------|---------------|-------------|--------------------|---------|
| Dr. Behr | L-glutathione | WE-11020045 | 20366              | 40      |
| Euro OTC | L-glutathione | 1102019-02  | 21788 <sup>†</sup> | 20      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 9 spectra from 3 *Apo-Ident* customers from 8 batches from the substance/substance group L-glutathione.

| Supplier | Substance     | Batch      | Spectra |
|----------|---------------|------------|---------|
| dr.behr  | L-glutathione | PF12E80201 | 2       |

*continued on the next page*

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier      | Substance     | Batch       | Spectra |
|---------------|---------------|-------------|---------|
| Dr. Behr GmbH | L-glutathione | WE14110006  | 1       |
| Euro OTC      | L-glutathione | 1102019-01  | 1       |
| Fagron        | L-glutathione | 11E02-N08   | 1       |
| Fagron        | L-glutathione | 14H21-B02   | 1       |
| dr.behr       | L-glutathione | WE11020045  | 1       |
| dr.behr       | L-glutathione | WE-12070001 | 1       |
| Dr. Behr GmbH | L-glutathione | WE14010014  | 1       |

- 69 624 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *L-glutathione* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *L-glutathione* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 59            | 1              | 146 669       |
| <b>Type C</b> | 0              | 9             | 0              | 69 624        |

The substance/substance group *L-glutathione* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 98.3333 % (> 93.3333 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21788     | 21788               | 0.00                         | 47.45                           |
| 23143     | 23143               | 0.00                         | 47.60                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Lidocaine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20942-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Lidocaine; Lidocainum

### Special notes

When selecting the *Lidocaine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Lidocaine*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Fagron   | Lidocaine | 13H05-N05        | 20942     | 40      | 1401378     |
| Euro OTC | Lidocaine | 1310023-01       | 21640     | 40      | 20131118    |
| Caelo    | Lidocaine | 13352411         | 21673     | 40      | 20131115    |
| Euro OTC | Lidocaine | 1612021          | 22984     | 40      | 20170206*   |
| Fagron   | Lidocaine | 16F21-B06-327232 | 23019     | 40      | 20160728    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Lidocaine*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 6 reference samples from the substance/substance group *Lidocaine*.

| Supplier    | Substance | Batch      | Sample ID          | Spectra |
|-------------|-----------|------------|--------------------|---------|
| zu erfassen | Lidocaine | pending    | 20148              | 40      |
| Euro OTC    | Lidocaine | 1310023-01 | 21640 <sup>†</sup> | 20      |
| Caelo       | Lidocaine | 13352411   | 21673 <sup>†</sup> | 20      |
| Euro OTC    | Lidocaine | 1603027    | 22526              | 40      |
| Caelo       | Lidocaine | 162895     | 22768              | 40      |
| Caelo       | Lidocaine | 171831     | 23632              | 40      |

- 146 529 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 320 spectra from 141 *Apo-Ident* customers from 129 batches from the substance/substance group *Lidocaine*.

| Supplier                | Substance | Batch       | Spectra |
|-------------------------|-----------|-------------|---------|
| Fagron                  | Lidocaine | 214U-03584  | 1       |
| Caelo                   | Lidocaine | 5111201     | 1       |
| Fagron                  | Lidocaine | 5122014A    | 1       |
| Fagron                  | Lidocaine | 515M-07006  | 1       |
| Fagron                  | Lidocaine | 6J23-No2    | 1       |
| Phönix 29.03.2012       | Lidocaine | 9205906     | 1       |
| Caelo                   | Lidocaine | 9205919     | 1       |
| Caelo                   | Lidocaine | 9205922     | 1       |
| Fagron                  | Lidocaine | 1113M-03584 | 1       |
| Fagron                  | Lidocaine | 11C09-N07   | 2       |
| Fagron                  | Lidocaine | 1116E-07006 | 1       |
| Fagron                  | Lidocaine | 11D28-N12   | 1       |
| Fagron                  | Lidocaine | 11K17-N03   | 2       |
| Fagron                  | Lidocaine | 12/21-N06   | 2       |
| Phönix, 12.11.2012      | Lidocaine | 12163801    | 1       |
| Euro OTC                | Lidocaine | 12163801    | 5       |
| Caelo                   | Lidocaine | 12163802    | 2       |
| Caelo                   | Lidocaine | 12163803    | 3       |
| Caelo                   | Lidocaine | 12163804    | 3       |
| Caelo                   | Lidocaine | 12163810    | 1       |
| Caelo                   | Lidocaine | 12163811    | 4       |
| Caelo                   | Lidocaine | 12163813    | 5       |
| Caesar/Lorenz           | Lidocaine | 12163813    | 1       |
| Henry Lamotte Oils GmbH | Lidocaine |             | 1       |
| Caelo                   | Lidocaine | 122294405   | 1       |
| Caelo                   | Lidocaine | 12294405    | 4       |
| Caelo                   | Lidocaine | 12294408    | 2       |
| Caelo                   | Lidocaine | 12294411    | 2       |
| Caelo                   | Lidocaine | 12294412    | 9       |
| Caesar & Loretz GmbH    | Lidocaine | 12294412    | 1       |
| Phönix 13.05.2013       | Lidocaine | 12B27-N04   | 1       |
| Phönix Gotha            | Lidocaine | 12C08-N11   | 1       |
| Fagron                  | Lidocaine | 12C08-N11   | 1       |
| Fagron                  | Lidocaine | 12c8-n11    | 1       |
| Fagron                  | Lidocaine | 12E30-N10   | 10      |
| Fargon                  | Lidocaine | 12E30-N10   | 1       |
| Anzag                   | Lidocaine | 12E30-N10   | 1       |
| Fagron                  | Lidocaine | 12h16n05    | 1       |
| Fagron                  | Lidocaine | 12H16-N05   | 8       |
| Fagron                  | Lidocaine | 12h16-N05   | 1       |
| Fagron                  | Lidocaine | 12H16-n05   | 1       |
| Sanacorp                | Lidocaine | 12H16-N05   | 1       |
| Noweda                  | Lidocaine | 12H16-N05   | 1       |
| Fagron                  | Lidocaine | 12I12-N06   | 1       |
| Gehe                    | Lidocaine | 12H16-N05   | 1       |
| Fagron                  | Lidocaine | 12I21N06    | 1       |
| Fagron                  | Lidocaine | 12I21-N06   | 3       |
| Sanacorp                | Lidocaine | 12I21-N06   | 1       |
| Anzag 07.03.2013        | Lidocaine | 12K13-N01   | 1       |
| Fagron                  | Lidocaine | 12K13-N01   | 3       |
| Euro OTC                | Lidocaine | 1310023-02  | 1       |
| Caelo                   | Lidocaine | 133524      | 1       |
| Caelo                   | Lidocaine | 13352403    | 1       |
| Caelo                   | Lidocaine | 13352405    | 2       |
| Caelo                   | Lidocaine | 13352406    | 1       |
| Caelo                   | Lidocaine | 13352408    | 8       |

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| Supplier                   | Substance | Batch             | Spectra |
|----------------------------|-----------|-------------------|---------|
| Caelo                      | Lidocaine | 13352411          | 6       |
| Caelo                      | Lidocaine | 13352413          | 3       |
| Caelo                      | Lidocaine | 13352414          | 2       |
| Caelo                      | Lidocaine | 13352415          | 2       |
| Fagron                     | Lidocaine | 13B27-N04         | 9       |
| Phönix                     | Lidocaine | 13B27-N04         | 1       |
| Fagron                     | Lidocaine | 13B27N04          | 1       |
| Fagron                     | Lidocaine | 13E28-B40-289433  | 1       |
| Fagron                     | Lidocaine | 13H05-N05         | 8       |
| Gehe am 22.01.2014         | Lidocaine | 13H05-N05         | 3       |
| Fargon/Phoenix             | Lidocaine | 13H05-N05         | 3       |
| Fagron                     | Lidocaine | 13H05-N050115/280 | 1       |
| Fagron                     | Lidocaine | 13H05-N050171/245 | 1       |
| Fagron                     | Lidocaine | 13J30-B02         | 6       |
| Fagron                     | Lidocaine | 13J30-b02-287639  | 1       |
| Fagron                     | Lidocaine | 13j30-B02-287639  | 1       |
| Fagron                     | Lidocaine | 13J30-B02-287640  | 1       |
| PHOENIX 22.08.2014         | Lidocaine | 13J30-B02-287640  | 1       |
| Fagron                     | Lidocaine | 13J30-B02-287641  | 5       |
| Fagron                     | Lidocaine | 13J30-B02-292219  | 3       |
| Fagron                     | Lidocaine | 13j30B02292219    | 1       |
| GEHE 02.12.2014            | Lidocaine | 13J30-B02-292220  | 1       |
| Fagron                     | Lidocaine | 13J30-B02-292220  | 2       |
| Fagron                     | Lidocaine | 13J30-B02-292221  | 6       |
| Caelo                      | Lidocaine | 13J30-B02-292221  | 1       |
| Caelo                      | Lidocaine | 14299301          | 3       |
| Caelo                      | Lidocaine | 14299303          | 2       |
| Caelo                      | Lidocaine | 14299305          | 2       |
| Fagron                     | Lidocaine | 14E13-B05         | 3       |
| Fagron                     | Lidocaine | 14E13-B05-295549  | 3       |
| Fagron                     | Lidocaine | 14E13-B05-295550  | 3       |
| Gehe Kassel                | Lidocaine | 14E13-B05-295550  | 1       |
| Fagron                     | Lidocaine | 14E13-B05-295552  | 2       |
| Fargron                    | Lidocaine | 14E13-B05-295552  | 1       |
| Caelo                      | Lidocaine | 1512003           | 1       |
| Caelo                      | Lidocaine | 15212001          | 2       |
| Caelo                      | Lidocaine | 15212002          | 5       |
| Caelo                      | Lidocaine | 15212003          | 3       |
| Caelo                      | Lidocaine | 15332302          | 1       |
| Caelo                      | Lidocaine | 15332303          | 1       |
| Rondell Apotheke           | Lidocaine | 15332304          | 1       |
| Moehs BCN S.L. / Noweda    | Lidocaine | 15332305          | 1       |
| Phoenix                    | Lidocaine | 15332305          | 1       |
| Caelo                      | Lidocaine | 15332305          | 2       |
| Caelo                      | Lidocaine | 15332306          | 1       |
| Caelo                      | Lidocaine | 15332309          | 2       |
| Caelo                      | Lidocaine | 15332310          | 2       |
| Caelo                      | Lidocaine | 15332314          | 2       |
| Caesar&Loretz,Phönix,06... | Lidocaine | 15332314          | 1       |
| Fagron                     | Lidocaine | 15A15-01-304282   | 1       |
| Fagron                     | Lidocaine | 15A15-B01         | 2       |
| Fagron                     | Lidocaine | 15A15-B01-304282  | 3       |
| Fagron                     | Lidocaine | 15A15-B01-304283  | 2       |
| Phönix Gotha               | Lidocaine | 15A15-B01-304284  | 1       |
| Fagron                     | Lidocaine | 15A15B01304284    | 1       |
| Caelo                      | Lidocaine | 15A15-B01-304284  | 2       |
| Fagron                     | Lidocaine | 15A15-B01-304284  | 4       |
| Fagron                     | Lidocaine | 15D23-B08         | 1       |
| Caelo                      | Lidocaine | 15D23-B08         | 1       |
| Fagron                     | Lidocaine | 15D23-B08309882   | 1       |

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| Supplier                   | Substance | Batch             | Spectra |
|----------------------------|-----------|-------------------|---------|
| Fagron                     | Lidocaine | 15D23-B08312058   | 1       |
| Fagron                     | Lidocaine | 15d23-b08-309882  | 1       |
| Fagron                     | Lidocaine | 15D23B08311708    | 1       |
| Fagron                     | Lidocaine | 15D23-B08-309882  | 1       |
| Fagron                     | Lidocaine | 15D23-B08-312058  | 4       |
| Fagron                     | Lidocaine | 15H27-B07         | 1       |
| Fagron                     | Lidocaine | 15H27-B07-315483  | 2       |
| Caelo                      | Lidocaine | 15H27-B07-318310  | 1       |
| Euro OTC                   | Lidocaine | 1603027-01        | 2       |
| Caelo                      | Lidocaine | 16087702          | 1       |
| Caelo                      | Lidocaine | 16087704          | 5       |
| Caelo                      | Lidocaine | 16087707          | 3       |
| Caesar & Loretz GmbH Hi... | Lidocaine | 16087709          | 1       |
| Caelo                      | Lidocaine | 16087711          | 2       |
| Caelo                      | Lidocaine | 16087712          | 3       |
| Caelo                      | Lidocaine | 16289502          | 3       |
| Ebert-Jacobi               | Lidocaine | 16289504          | 1       |
| Caelo                      | Lidocaine | 16289504          | 1       |
| Fagron                     | Lidocaine | 16A28-B06         | 1       |
| Caelo                      | Lidocaine | 16A28-B06-320059  | 1       |
| Fagron                     | Lidocaine | 16A28-B06-320059  | 2       |
| Fagron                     | Lidocaine | 16A-28-B06-321297 | 1       |
| Alte Apotheke              | Lidocaine | 16A28B06-321297   | 1       |
| Fagron                     | Lidocaine | 16F21-B06         | 3       |
| Fagron                     | Lidocaine | 16F21-B06-323670  | 4       |
| Fagron                     | Lidocaine | 16F21-B06-325934  | 1       |
| Fagron                     | Lidocaine | 16F21B06325934    | 1       |
| Fagron                     | Lidocaine | 16F21-B06-328421  | 1       |
| Caelo                      | Lidocaine | 16F21-B06-328421  | 1       |
| Fagron                     | Lidocaine | 16F21-B06-332253  | 1       |
| Caelo                      | Lidocaine | 2811M-03584       | 1       |
| Fagron                     | Lidocaine | 312/1             | 1       |
| Fagron                     | Lidocaine |                   | 2       |
| PHOENIX 22.08.2014         | Lidocaine |                   | 2       |
| Noweda                     | Lidocaine | 5308e-07003       | 1       |
| Gehe 09.07.2013            | Lidocaine | 8565948           | 1       |
| Fagron                     | Lidocaine | 5742              | 1       |
| Caelo                      | Lidocaine | 8629595           | 1       |
| Fagron                     | Lidocaine | 700412-0004       | 1       |
| Fagron                     | Lidocaine | 1014I-07006       | 1       |
| Caelo                      | Lidocaine | 11K17-N03         | 1       |
| Caelo                      | Lidocaine | 12H16-N05         | 1       |
| Gutenberg-Apotheke         | Lidocaine | 13J30-B02         | 1       |
| Fagron                     | Lidocaine | 15d23-b08-312058  | 1       |
| Caelo                      | Lidocaine | 16087709          | 1       |

- 69 313 spectra from 414 *Apo-Ident* customers from a total of 23 675 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Lidocaine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all

relevant spectra of the various substances were compared with *Lidocaine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 200           | 0              | 71 186        |
| Type B | 0              | 190           | 10             | 146 529       |
| Type C | 0              | 319           | 1              | 69 313        |

The substance/substance group *Lidocaine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 95.0000 % (> 93.5000 %)  |
| Type C | 100.0000 % (> 99.8812 %) | 99.6875 % (> 98.7500 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20942     | 20942               | 0.00                         | 43.16                           |
| 21640     | 22984               | 6.06                         | 44.02                           |
| 21673     | 22984               | 18.83                        | 43.39                           |
| 22984     | 22984               | 0.00                         | 40.07                           |
| 23019     | 22984               | 3.18                         | 37.99                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Lidocaine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20093-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Lidocaine hydrochloride; Lidocaini hydrochloridum; Lidocainum hydrochloricum

### Special notes

When selecting the *Lidocaine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Lidocaine hydrochloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------|-----------|---------|--------------------|
| Caelo    | Lidocaine hydroc... | 12135511   | 20882     | 40      | AR-15-FG-008867-01 |
| Euro OTC | Lidocaine hydroc... | 1403025-02 | 21613     | 40      | 20140516           |
| Euro OTC | Lidocaine hydroc... | 1411010    | 21770     | 40      | 0000009260         |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Lidocaine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 7 reference samples from the substance/substance group *Lidocaine hydrochloride*.

| Supplier | Substance               | Batch      | Sample ID          | Spectra |
|----------|-------------------------|------------|--------------------|---------|
| Euro OTC | Lidocaine hydrochloride | 1403025-02 | 21613 <sup>†</sup> | 20      |
| Euro OTC | Lidocaine hydrochloride | 1411010    | 21770 <sup>†</sup> | 20      |
| Euro OTC | Lidocaine hydrochloride | 1606024    | 22702              | 40      |
| Caelo    | Lidocaine hydrochloride | 162222     | 22771              | 40      |
| Caelo    | Lidocaine hydrochloride | 152995     | 22772              | 40      |
| Euro OTC | Lidocaine hydrochloride | 1612015    | 22980              | 40      |
| Caelo    | Lidocaine hydrochloride | 172048     | 23687              | 40      |

- 146 489 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 732 spectra from 249 *Apo-Ident* customers from 177 batches from the substance/substance group *Lidocaine hydrochloride*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier             | Substance               | Batch            | Spectra |
|----------------------|-------------------------|------------------|---------|
| Euro OTC             | Lidocaine hydrochloride | 1202035-01       | 30      |
| Caelo                | Lidocaine hydrochloride | 1010024-01       | 2       |
| Euro OTC             | Lidocaine hydrochloride | 1108017-01       | 8       |
| Euro OTC             | Lidocaine hydrochloride | 120203501        | 2       |
| Euro OTC             | Lidocaine hydrochloride | 1202035-02       | 51      |
| Euro OTC             | Lidocaine hydrochloride | 1202035-03       | 14      |
| Konduskar/Phönix     | Lidocaine hydrochloride | 1202035-03       | 1       |
| Caelo                | Lidocaine hydrochloride | 12021503         | 1       |
| Caelo                | Lidocaine hydrochloride | 13118807         | 6       |
| Caelo                | Lidocaine hydrochloride | 12176103         | 9       |
| Caelo                | Lidocaine hydrochloride | 13118803         | 6       |
| Caelo                | Lidocaine hydrochloride | 13118808         | 5       |
| Caelo                | Lidocaine hydrochloride | 13118811         | 2       |
| Caelo                | Lidocaine hydrochloride | 13343001         | 2       |
| Caelo                | Lidocaine hydrochloride | 13118812         | 2       |
| Caelo                | Lidocaine hydrochloride | 13343002         | 5       |
| Caelo                | Lidocaine hydrochloride |                  | 1       |
| Caesar & Loretz GmbH | Lidocaine hydrochloride | 13343002         | 1       |
| Caelo                | Lidocaine hydrochloride | 13343003         | 5       |
| Caelo                | Lidocaine hydrochloride | 13343004         | 7       |
| Caelo                | Lidocaine hydrochloride | 13343007         | 14      |
| Euro OTC             | Lidocaine hydrochloride |                  | 3       |
| Caelo                | Lidocaine hydrochloride | 13343008         | 3       |
| Caelo                | Lidocaine hydrochloride | 13343011         | 3       |
| Caelo                | Lidocaine hydrochloride | 13343012         | 15      |
| Caelo                | Lidocaine hydrochloride | 13343014         | 5       |
| Caelo                | Lidocaine hydrochloride | 13343015         | 3       |
| Caelo                | Lidocaine hydrochloride | 13343016         | 2       |
| Caelo                | Lidocaine hydrochloride | 13343017         | 5       |
| Caesar u Loretz      | Lidocaine hydrochloride | 13343017         | 1       |
| Caelo                | Lidocaine hydrochloride | 13343019         | 5       |
| Fagron               | Lidocaine hydrochloride | 13F07-N06        | 9       |
| Fagron               | Lidocaine hydrochloride | 13L18-B11-286901 | 1       |
| Fagron               | Lidocaine hydrochloride | 13L18-B11        | 1       |
| Euro OTC             | Lidocaine hydrochloride | 1401010-01       | 1       |
| Euro OTC             | Lidocaine hydrochloride | 1403025-01       | 16      |
| Euro OTC             | Lidocaine hydrochloride | 140302501        | 3       |
| PHOENIX 17.06.2014   | Lidocaine hydrochloride | 1403025-01       | 1       |
| Euro OTC             | Lidocaine hydrochloride | 1403025-02       | 16      |
| Caelo                | Lidocaine hydrochloride | 1403025-02       | 3       |
| Euro OTC             | Lidocaine hydrochloride | 140302502        | 1       |
| Euro OTC             | Lidocaine hydrochloride | 1403025-03       | 1       |
| Euro OTC             | Lidocaine hydrochloride | 140415A          | 1       |
| Euro OTC             | Lidocaine hydrochloride | 1411010-01       | 30      |
| Euro OTC             | Lidocaine hydrochloride | 141101001        | 2       |
| Caelo                | Lidocaine hydrochloride | 1411010-01       | 2       |
| Gehe                 | Lidocaine hydrochloride | 1411010-01       | 1       |
| Euro OTC             | Lidocaine hydrochloride | 1411010-01Mg25g  | 1       |
| Euro OTC             | Lidocaine hydrochloride | 1411010-02       | 16      |
| Phönix Gotha         | Lidocaine hydrochloride | 1411010-02       | 1       |
| Caelo                | Lidocaine hydrochloride | 1411010-02       | 1       |
| Euro OTC             | Lidocaine hydrochloride | 1411010-02Mg50g  | 1       |
| Euro OTC             | Lidocaine hydrochloride | 141101-01        | 1       |
| Euro OTC             | Lidocaine hydrochloride | 14110101-01      | 1       |
| Euro/Phönix          | Lidocaine hydrochloride | 141101010-01     | 1       |
| Euro OTC             | Lidocaine hydrochloride | 1411010-2        | 1       |
| Caelo                | Lidocaine hydrochloride | 14254001         | 3       |
| Fagron               | Lidocaine hydrochloride | 14B12-B03        | 2       |
| Fagron               | Lidocaine hydrochloride | 14B12-B03-292214 | 7       |
| Alliance health      | Lidocaine hydrochloride | 14B12-B03-292214 | 1       |

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| Supplier                  | Substance               | Batch            | Spectra |
|---------------------------|-------------------------|------------------|---------|
| Fagron                    | Lidocaine hydrochloride | 14B12-B03-292218 | 1       |
| Fagron                    | Lidocaine hydrochloride | 14E13-B06-294975 | 5       |
| Fagron                    | Lidocaine hydrochloride | 14e13-b06-294975 | 1       |
| Fagron                    | Lidocaine hydrochloride | 14J07-B04-299433 | 3       |
| Fagron                    | Lidocaine hydrochloride | 14J07-B04-299434 | 2       |
| Fagron                    | Lidocaine hydrochloride | 14J20-B05        | 1       |
| Fagron                    | Lidocaine hydrochloride | 14J20-B05-303131 | 1       |
| Caelo                     | Lidocaine hydrochloride | 14J20-B05-303133 | 1       |
| Fagron                    | Lidocaine hydrochloride | 14J20-B05-303133 | 2       |
| Fagron                    | Lidocaine hydrochloride | 15/17-B01-316805 | 1       |
| Mahendra Chem./Noweda     | Lidocaine hydrochloride | 1505023          | 1       |
| Euro OTC                  | Lidocaine hydrochloride | 1505023-01       | 39      |
| Caelo                     | Lidocaine hydrochloride | 1505023-01       | 4       |
| Fagron                    | Lidocaine hydrochloride | 1505023-01       | 2       |
| Euro OTC                  | Lidocaine hydrochloride | 150502301        | 1       |
| Euro OTC                  | Lidocaine hydrochloride | 1505023-02       | 12      |
| Sanacorp                  | Lidocaine hydrochloride | 150502302        | 1       |
| Caelo                     | Lidocaine hydrochloride | 1505023-03       | 2       |
| Euro OTC                  | Lidocaine hydrochloride | 1505023-03       | 9       |
| Euro/Alliance Healthcare  | Lidocaine hydrochloride | 150523-01        | 1       |
| Caelo                     | Lidocaine hydrochloride | 1515I-01775      | 1       |
| Caelo                     | Lidocaine hydrochloride | 1521304          | 1       |
| Caelo                     | Lidocaine hydrochloride | 1517-B01-315828  | 1       |
| Caelo                     | Lidocaine hydrochloride | 15215201         | 3       |
| Caesar & Loretz GmbH      | Lidocaine hydrochloride | 15215201         | 1       |
| Caelo                     | Lidocaine hydrochloride | 15215301         | 5       |
| Bombastus                 | Lidocaine hydrochloride | 15215301         | 1       |
| Caelo                     | Lidocaine hydrochloride | 15215302         | 2       |
| Caesar&Loretz GmbH /Anzag | Lidocaine hydrochloride | 15215303         | 1       |
| Caelo                     | Lidocaine hydrochloride | 15215303         | 2       |
| Caelo                     | Lidocaine hydrochloride | 15215304         | 3       |
| Gehe                      | Lidocaine hydrochloride | 15215304         | 1       |
| Rondell Apotheke          | Lidocaine hydrochloride | 15215308         | 1       |
| Caelo                     | Lidocaine hydrochloride | 15215308         | 2       |
| Caelo                     | Lidocaine hydrochloride | 15215309         | 1       |
| Caelo                     | Lidocaine hydrochloride | 15215310         | 8       |
| Caelo                     | Lidocaine hydrochloride | 15215311         | 3       |
| Fagron                    | Lidocaine hydrochloride | 15215311         | 2       |
| Caelo                     | Lidocaine hydrochloride | 15215312         | 5       |
| Sanacorp                  | Lidocaine hydrochloride | 15215312         | 1       |
| Caelo                     | Lidocaine hydrochloride | 152951602714117  | 1       |
| Caelo                     | Lidocaine hydrochloride | 15299503         | 7       |
| Caelo                     | Lidocaine hydrochloride | 15299506         | 2       |
| Caelo                     | Lidocaine hydrochloride | 15299509         | 2       |
| Caelo                     | Lidocaine hydrochloride | 15299513         | 1       |
| Caelo                     | Lidocaine hydrochloride | 15299514         | 3       |
| Caelo                     | Lidocaine hydrochloride | 15299516         | 2       |
| Fagron                    | Lidocaine hydrochloride | 15I17-B01-315828 | 1       |
| Caelo                     | Lidocaine hydrochloride | 160113           | 1       |
| Euro OTC                  | Lidocaine hydrochloride | 1600024-02       | 1       |
| Euro OTC                  | Lidocaine hydrochloride | 1606021-01       | 1       |
| Euro OTC                  | Lidocaine hydrochloride | 1606024-01       | 22      |
| Euro OTC                  | Lidocaine hydrochloride | 160602401        | 1       |
| Ensbona/ Sanacorp         | Lidocaine hydrochloride | 1606024-01       | 1       |
| Swati / Noweda            | Lidocaine hydrochloride | 1606024-01       | 1       |
| Alte Apotheke             | Lidocaine hydrochloride | 1606024-01       | 2       |
| Caelo                     | Lidocaine hydrochloride | 1606024-01       | 9       |
| Euro OTC                  | Lidocaine hydrochloride | 1606024-02       | 14      |
| Caelo                     | Lidocaine hydrochloride | 1606024-02       | 1       |
| Gehe                      | Lidocaine hydrochloride | 1606024-02       | 1       |

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| Supplier                   | Substance               | Batch            | Spectra |
|----------------------------|-------------------------|------------------|---------|
| Caelo                      | Lidocaine hydrochloride | 160602402        | 1       |
| Caelo                      | Lidocaine hydrochloride | 16101407         | 1       |
| Euro OTC                   | Lidocaine hydrochloride | 1612015-01       | 2       |
| Euro OTC                   | Lidocaine hydrochloride | 1606024-03       | 1       |
| Caelo                      | Lidocaine hydrochloride | 16222203         | 1       |
| Caelo                      | Lidocaine hydrochloride | 168020-0003      | 1       |
| Fagron                     | Lidocaine hydrochloride | 16C09-B03        | 1       |
| Fagron                     | Lidocaine hydrochloride | 16J24-B15-329421 | 1       |
| Fagron                     | Lidocaine hydrochloride | 17A16-B07-333010 | 1       |
| Caelo                      | Lidocaine hydrochloride | 18041501         | 1       |
| Caelo                      | Lidocaine hydrochloride | 1912M-01775      | 1       |
| Euro OTC                   | Lidocaine hydrochloride | 23081601         | 1       |
| Caelo                      | Lidocaine hydrochloride | 26041401         | 1       |
| Caelo                      | Lidocaine hydrochloride | 24071401         | 1       |
| Caelo                      | Lidocaine hydrochloride | 280501           | 1       |
| Fagron                     | Lidocaine hydrochloride | 4612Q-01775      | 1       |
| Caelo                      | Lidocaine hydrochloride | 29081503         | 1       |
| Caelo                      | Lidocaine hydrochloride | 5113E-01775      | 1       |
| Moehs Catalana, S.L./Ph... | Lidocaine hydrochloride |                  | 1       |
| Swati/Noweda               | Lidocaine hydrochloride | LDH/116007       | 1       |
| Caelo                      | Lidocaine hydrochloride | 2051301          | 1       |
| Alliance Health 08.03.2... | Lidocaine hydrochloride | 1010024-01       | 1       |
| Fagron                     | Lidocaine hydrochloride | 9E08-N03         | 1       |
| Fagron                     | Lidocaine hydrochloride | 8F26-N07         | 1       |
| Caelo                      | Lidocaine hydrochloride | 4111302          | 1       |
| Caelo                      | Lidocaine hydrochloride | 10320703         | 1       |
| Caelo                      | Lidocaine hydrochloride | 10320717         | 1       |
| Caelo                      | Lidocaine hydrochloride | 10320704         | 1       |
| Caelo                      | Lidocaine hydrochloride | 10320707         | 1       |
| Noweda                     | Lidocaine hydrochloride | 11/19-N06        | 1       |
| Caelo                      | Lidocaine hydrochloride | 10320719         | 1       |
| Euro OTC                   | Lidocaine hydrochloride | 1103034-01       | 2       |
| Noweda                     | Lidocaine hydrochloride | 1108017-01       | 1       |
| Euro OTC                   | Lidocaine hydrochloride | 1108017-02       | 9       |
| Noweda                     | Lidocaine hydrochloride | 1108017-02       | 1       |
| EuRho/Phoenix              | Lidocaine hydrochloride | 1108017-02       | 1       |
| Caelo                      | Lidocaine hydrochloride | 113002905        | 1       |
| Caelo                      | Lidocaine hydrochloride | 11091203         | 1       |
| Caelo                      | Lidocaine hydrochloride | 11302902         | 2       |
| Caelo                      | Lidocaine hydrochloride | 11302904         | 1       |
| Caelo                      | Lidocaine hydrochloride | 11302905         | 1       |
| Caelo                      | Lidocaine hydrochloride | 11302906         | 3       |
| Fagron                     | Lidocaine hydrochloride | 11H18-N01        | 2       |
| Fagron                     | Lidocaine hydrochloride | 11L09-N09        | 2       |
| Caelo                      | Lidocaine hydrochloride | 12020302         | 1       |
| Euro OTC                   | Lidocaine hydrochloride | 1202034-01       | 2       |
| Euro OTC                   | Lidocaine hydrochloride | 1202035          | 1       |
| Caelo                      | Lidocaine hydrochloride | 1202035          | 1       |
| Euro OTC                   | Lidocaine hydrochloride | 1202035/02       | 1       |
| Caelo                      | Lidocaine hydrochloride | 120203501        | 1       |
| Finze                      | Lidocaine hydrochloride | 1202035-01       | 1       |
| Gehe                       | Lidocaine hydrochloride | 1202035-01       | 1       |
| Sanacorp                   | Lidocaine hydrochloride | 1202035-01       | 3       |
| Caelo                      | Lidocaine hydrochloride | 1202035-02       | 2       |
| Euro OTC                   | Lidocaine hydrochloride | 120203502        | 4       |
| Gehe                       | Lidocaine hydrochloride | 1202035-02       | 1       |
| PHOENIX am 12.02.2014      | Lidocaine hydrochloride | 1202035-02       | 1       |
| Phönix                     | Lidocaine hydrochloride | 1202035-03       | 1       |
| Caelo                      | Lidocaine hydrochloride | 1202035-03       | 1       |
| Noweda                     | Lidocaine hydrochloride | 1202035-03       | 1       |

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| Supplier                 | Substance               | Batch            | Spectra |
|--------------------------|-------------------------|------------------|---------|
| Anzag                    | Lidocaine hydrochloride | 1202035-03       | 1       |
| Euro OTC                 | Lidocaine hydrochloride | 1202035-1        | 1       |
| Caelo                    | Lidocaine hydrochloride | 12135503         | 6       |
| Caelo                    | Lidocaine hydrochloride | 12135504         | 3       |
| Caelo                    | Lidocaine hydrochloride | 12135508         | 7       |
| Caelo                    | Lidocaine hydrochloride | 12135509         | 4       |
| Fiebig 04.7.13 EK 4,54   | Lidocaine hydrochloride | 12135511         | 1       |
| Großhandel               | Lidocaine hydrochloride | 12135511         | 1       |
| Caelo                    | Lidocaine hydrochloride | 12135511         | 3       |
| Caelo                    | Lidocaine hydrochloride | 12176101         | 8       |
| Caelo                    | Lidocaine hydrochloride | 12176102         | 10      |
| Caelo                    | Lidocaine hydrochloride | 12176109         | 2       |
| Gehe                     | Lidocaine hydrochloride | 12C05-N02        | 2       |
| Fagron                   | Lidocaine hydrochloride | 12c05-N02        | 1       |
| Fagron                   | Lidocaine hydrochloride | 12E14-N04        | 3       |
| Fagron                   | Lidocaine hydrochloride | 12H09-N08        | 3       |
| Caelo                    | Lidocaine hydrochloride | 13118802         | 2       |
| Fagron                   | Lidocaine hydrochloride | 12C05-N02        | 2       |
| Caesar&Loretz GmbH/Anzag | Lidocaine hydrochloride | 13118803         | 2       |
| Caelo                    | Lidocaine hydrochloride | 13118806         | 1       |
| Sanacorp                 | Lidocaine hydrochloride | 13118807         | 1       |
| Hedinger/Ebert           | Lidocaine hydrochloride | 13118807         | 1       |
| Caolo                    | Lidocaine hydrochloride | 13343008         | 1       |
| Fagron                   | Lidocaine hydrochloride | 13F07N06         | 1       |
| EuRho                    | Lidocaine hydrochloride | 140302501        | 1       |
| Europ Ots Pharma         | Lidocaine hydrochloride | 1403025-01       | 1       |
| Fagron                   | Lidocaine hydrochloride | 14e13-b06-294973 | 1       |
| Euro OTC                 | Lidocaine hydrochloride | 20131010-4       | 1       |
| Euro OTC                 | Lidocaine hydrochloride | 2213U01775       | 1       |
| Caelo                    | Lidocaine hydrochloride | 23011403         | 1       |
| Caelo                    | Lidocaine hydrochloride | 25091202         | 1       |
| Euro OTC                 | Lidocaine hydrochloride | 2805016-01       | 1       |
| Euro OTC                 | Lidocaine hydrochloride | 2810029-01       | 1       |
| Euro OTC                 | Lidocaine hydrochloride | 2911029-01       | 1       |
| Caelo                    | Lidocaine hydrochloride | 72702128         | 1       |
| Caelo                    | Lidocaine hydrochloride | 5211E-01775      | 1       |
| Fagron                   | Lidocaine hydrochloride | 9B3M1L2Fo118     | 1       |
| Caelo                    | Lidocaine hydrochloride | AKD14            | 1       |
| Euro OTC                 | Lidocaine hydrochloride | LID-20-11-001    | 2       |
| Fagron                   | Lidocaine hydrochloride | 13L18-B11-286903 | 1       |
| Caelo                    | Lidocaine hydrochloride | 14110101         | 1       |
| Caelo                    | Lidocaine hydrochloride | 1606024          | 1       |
| Fagron                   | Lidocaine hydrochloride | 15I17-B01-316805 | 1       |
| 01.07.14                 | Lidocaine hydrochloride | 13343004         | 1       |
| Euro OTC                 | Lidocaine hydrochloride | 141101002        | 1       |
| Caelo                    | Lidocaine hydrochloride | 1814U-01775      | 1       |
| Caelo                    | Lidocaine hydrochloride | P155/14          | 1       |
| Euro/phönix              | Lidocaine hydrochloride | 1202035-01       | 2       |
| A.H.D.                   | Lidocaine hydrochloride | 1202035-02       | 1       |
| Caelo                    | Lidocaine hydrochloride | 26071303         | 1       |
| Großhandel               | Lidocaine hydrochloride | 13343002         | 1       |

- 68 901 spectra from 413 *Apo-Ident* customers from a total of 23 628 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Lidocaine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Lidocaine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 240           | 0              | 146 489       |
| <b>Type C</b> | 0              | 706           | 26             | 68 901        |

The substance/substance group *Lidocaine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 96.4481 % (> 96.0383 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20882     | 20882               | 0.00                         | 46.54                           |
| 21613     | 20882               | 7.61                         | 45.16                           |
| 21770     | 21770               | 0.00                         | 49.27                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **L-isoleucine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21045-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

L-isoleucine; L-Isoleucinum

### Special notes

When selecting the *L-isoleucine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *L-isoleucine*:

| Supplier | Substance    | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------|------------------|-----------|---------|-------------|
| Fagron   | L-isoleucine | 13E02-B01-286930 | 21045     | 40      | 1403154     |
| Fagron   | L-isoleucine | 13E02-B01        | 21332     | 40      | 20130621    |
| Euro OTC | L-isoleucine | 1604057          | 22566     | 40      | 20160601*   |
| Euro OTC | L-isoleucine | 1704022          | 23386     | 40      | 20170612*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *L-isoleucine*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 5 reference samples from the substance/substance group *L-isoleucine*.

| Supplier | Substance    | Batch       | Sample ID | Spectra |
|----------|--------------|-------------|-----------|---------|
| Fagron   | L-isoleucine | 11F30-N06   | 20417     | 40      |
| Euro OTC | L-isoleucine | L1211010-02 | 21535     | 60      |
| Euro OTC | L-isoleucine | L1211010-02 | 21581     | 60      |
| Euro OTC | L-isoleucine | 1611007     | 22869     | 40      |
| Euro OTC | L-isoleucine | 1708027     | 23702     | 40      |

- 146 489 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 9 spectra from 6 *Apo-Ident* customers from 9 batches from the substance/substance group *L-isoleucine*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier | Substance    | Batch            | Spectra |
|----------|--------------|------------------|---------|
| Fagron   | L-isoleucine | 12H30-N03        | 1       |
| Fagron   | L-isoleucine | 13E02-B01-286930 | 1       |
| Fagron   | L-isoleucine | 13E02-B01-291112 | 1       |
| Fagron   | L-isoleucine | 15A14-B09        | 1       |
| Fagron   | L-isoleucine | 11C31-N07        | 1       |
| Fagron   | L-isoleucine | 12080167         | 1       |
| Fagron   | L-isoleucine | 121101           | 1       |
| Fagron   | L-isoleucine | 13A22-N03        | 1       |
| Fagron   | L-isoleucine | 8166210302       | 1       |

- 69 624 spectra from 414 *Apo-Ident* customers from a total of 23 792 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *L-isoleucine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *L-isoleucine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 203           | 37             | 146 489       |
| <b>Type C</b> | 0              | 9             | 0              | 69 624        |

The substance/substance group *L-isoleucine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 84.5833 % (> 83.3333 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21045     | 21045               | 0.00                         | 38.34                           |
| 21332     | 21045               | 4.80                         | 37.20                           |
| 22566     | 22566               | 0.00                         | 39.50                           |
| 23386     | 23386               | 0.00                         | 33.90                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Lithium orotate monohydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21055-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Lithium orotate monohydrate; Lithii orotas monohydricim

### Special notes

When selecting the *Lithium orotate monohydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Lithium orotate monohydrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Lithium orotate ... | 13J04-N01        | 21055     | 40      | 1405616     |
| Fagron   | Lithium orotate ... | 13I09-B04-290311 | 21688     | 40      | 20130927    |
| Fagron   | Lithium orotate ... | 15F25-B01-315219 | 22502     | 40      | 20150716    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Lithium orotate monohydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *Lithium orotate monohydrate*.

| Supplier | Substance                   | Batch            | Sample ID          | Spectra |
|----------|-----------------------------|------------------|--------------------|---------|
| Fagron   | Lithium orotate monohydrate | 10F25-N01        | 20437              | 40      |
| Fagron   | Lithium orotate monohydrate | 13I09-B04-290311 | 21688 <sup>†</sup> | 20      |
| Fagron   | Lithium orotate monohydrate | 16D15-B08-321402 | 23269              | 40      |

- 146 629 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 7 spectra from 2 *Apo-Ident* customers from 3 batches from the substance/substance group *Lithium orotate monohydrate*.

| Supplier    | Substance                   | Batch    | Spectra |
|-------------|-----------------------------|----------|---------|
| Pharmorgana | Lithium orotate monohydrate | ORL00212 | 4       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

continued from previous page

| Supplier       | Substance                   | Batch     | Spectra |
|----------------|-----------------------------|-----------|---------|
| Pfannenschmidt | Lithium orotate monohydrate | 0RL00212  | 1       |
| Microsin       | Lithium orotate monohydrate | 0RL00315  | 1       |
| Fagron         | Lithium orotate monohydrate | 13J04-N01 | 1       |

- 69 626 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Lithium orotate monohydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Lithium orotate monohydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 100           | 0              | 146 629       |
| <b>Type C</b> | 0              | 7             | 0              | 69 626        |

The substance/substance group *Lithium orotate monohydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21055     | 21055               | 0.00                         | 78.97                           |
| 21688     | 21055               | 4.01                         | 78.33                           |
| 22502     | 21055               | 14.74                        | 79.76                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **L-leucine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20970-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

L-leucine; Leucinum

### Special notes

When selecting the *L-leucine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *L-leucine*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Fagron   | L-leucine | 13J09-N03        | 20970     | 40      | 1402431     |
| Euro OTC | L-leucine | 1302013-01       | 21612     | 40      | 20130320    |
| Euro OTC | L-leucine | 1601032          | 22380     | 40      | 20160308*   |
| Fagron   | L-leucine | 15D09-B06-322249 | 23199     | 40      | 20151030    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group L-leucine. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group L-leucine.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Fagron   | L-leucine | 9D27-N04   | 20443              | 40      |
| Euro OTC | L-leucine | 1302013-01 | 21612 <sup>†</sup> | 20      |
| Euro OTC | L-leucine | 1708010    | 23607              | 40      |

- 146 629 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 5 spectra from 3 *Apo-Ident* customers from 4 batches from the substance/substance group L-leucine.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance | Batch       | Spectra |
|----------|-----------|-------------|---------|
| Euro OTC | L-leucine | 1312032-01  | 2       |
| Euro OTC | L-leucine | L1208003-01 | 1       |
| Fargon   | L-leucine | 8160410903  | 1       |
| Fargon   | L-leucine | 13J09-N03   | 1       |

- 69 628 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *L-leucine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *L-leucine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 83            | 17             | 146 629       |
| <b>Type C</b> | 0              | 4             | 1              | 69 628        |

The substance/substance group *L-leucine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 83.0000 % (> 80.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8815 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20970     | 20970               | 0.00                         | 66.67                           |

*continued on the next page*

*continued from previous page*

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21612            | 20970                      | 9.18                                | 67.05                                  |
| 22380            | 22380                      | 0.00                                | 59.52                                  |
| 23199            | 22380                      | 15.48                               | 52.80                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **L-malic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22357-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

L-malic acid; Acidum-(L)-malicum

### Special notes

When selecting the *L-malic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *L-malic acid*:

| Supplier | Substance    | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------|------------------|-----------|---------|-------------|
| Fagron   | L-malic acid | 15J09-B03-313987 | 22357     | 40      | 9346        |
| Fagron   | L-malic acid | 15J09-B03-313987 | 22730     | 40      | 20151106    |
| Fagron   | L-malic acid | 16J06-B98-327269 | 23107     | 40      | 20161117    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *L-malic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *L-malic acid*.

| Supplier | Substance    | Batch            | Sample ID          | Spectra |
|----------|--------------|------------------|--------------------|---------|
| Fagron   | L-malic acid | 15J09-B03-313987 | 22357 <sup>†</sup> | 20      |
| Fagron   | L-malic acid | 15J09-B03-313987 | 22612              | 40      |
| Fagron   | L-malic acid | 16J06-B98-327269 | 23222              | 40      |

- 146 629 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *L-malic acid*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *L-malic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *L-malic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 100           | 0              | 146 629       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *L-malic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22357     | 22357               | 0.00                         | 87.87                           |
| 22730     | 22357               | 3.98                         | 85.86                           |
| 23107     | 22357               | 1.92                         | 87.34                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **L-phenylalanine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21661-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

L-phenylalanine; Phenylalaninum

### Special notes

When selecting the *L-phenylalanine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *L-phenylalanine*:

| Supplier | Substance       | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------------|------------|-----------|---------|-------------|
| Caelo    | L-phenylalanine | 14088304   | 21661     | 40      | 1501656     |
| Euro OTC | L-phenylalanine | 1212014-03 | 21681     | 40      | 20130111    |
| Euro OTC | L-phenylalanine | 1704003    | 23173     | 40      | 20170425*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *L-phenylalanine*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 92 spectra of 4 reference samples from the substance/substance group *L-phenylalanine*.

| Supplier | Substance       | Batch      | Sample ID          | Spectra |
|----------|-----------------|------------|--------------------|---------|
| Caelo    | L-phenylalanine | 14088304   | 21661 <sup>†</sup> | 20      |
| Euro OTC | L-phenylalanine | 1212014-03 | 21681 <sup>†</sup> | 20      |
| Euro OTC | L-phenylalanine | 1409013-02 | 23024              | 40      |
| Euro OTC | L-phenylalanine | 1409013-02 | not required       | 12      |

- 146 637 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *L-phenylalanine*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *L-phenylalanine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *L-phenylalanine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 92            | 0              | 146 637       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *L-phenylalanine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 93.4783 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21661     | 21661               | 0.00                         | 44.62                           |
| 21681     | 23173               | 10.08                        | 56.65                           |
| 23173     | 23173               | 0.00                         | 66.42                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **L-proline**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21034-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

L-proline; Prolinum

### Special notes

When selecting the *L-proline* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *L-proline*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Fagron   | L-proline | 15D13-B02-308152 | 22270     | 40      | 1704059     |
| Euro OTC | L-proline | 1606010          | 22677     | 40      | 20160714*   |
| Fagron   | L-proline | 16J14-B01-327195 | 23109     | 40      | 20161116    |
| Euro OTC | L-proline | 1705021          | 23546     | 40      | 20170720*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *L-proline*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 280 spectra of 7 reference samples from the substance/substance group *L-proline*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Dr. Behr | L-proline | P-07014859       | 20368              | 40      |
| Euro OTC | L-proline | L1210046-02      | 21034              | 40      |
| Euro OTC | L-proline | L1210046-02      | 21075              | 60      |
| Euro OTC | L-proline | L1210046-01      | 21103              | 40      |
| Fagron   | L-proline | 15D13-B02-308152 | 22270 <sup>†</sup> | 20      |
| Euro OTC | L-proline | 1606010-01       | 23013              | 40      |
| Euro OTC | L-proline | 1606010-01       | 23100              | 40      |

- 146 449 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 4 spectra from 2 *Apo-Ident* customers from 3 batches from the substance/substance group *L-proline*.

| Supplier | Substance | Batch       | Spectra |
|----------|-----------|-------------|---------|
| Euro OTC | L-proline | 1312029-01  | 1       |
| Euro OTC | L-proline | L1210046-03 | 2       |
| Euro OTC | L-proline | L1210045-01 | 1       |

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *L-proline* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *L-proline* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 203           | 77             | 146 449       |
| <b>Type C</b> | 0              | 4             | 0              | 69 629        |

The substance/substance group *L-proline* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 72.5000 % (> 71.4286 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22270     | 22270               | 0.00                         | 62.24                           |
| 22677     | 22677               | 0.00                         | 70.89                           |
| 23109     | 22270               | 3.48                         | 64.26                           |
| 23546     | 23546               | 0.00                         | 49.13                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **L-serine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22289-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

L-serine; Serinum

### Special notes

When selecting the *L-serine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *L-serine*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Euro OTC | L-serine  | 1512012    | 22289     | 40      | 20160112*   |
| Euro OTC | L-serine  | 1606020-01 | 22668     | 40      | 20160714    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *L-serine*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *L-serine*.

| Supplier | Substance | Batch   | Sample ID          | Spectra |
|----------|-----------|---------|--------------------|---------|
| Euro OTC | L-serine  | 1512012 | 22289 <sup>†</sup> | 20      |
| Euro OTC | L-serine  | 1606020 | 22678              | 40      |
| Euro OTC | L-serine  | 1611006 | 22922              | 40      |

- 146 629 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 3 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *L-serine*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance | Batch      | Spectra |
|----------|-----------|------------|---------|
| Euro OTC | L-serine  | 1606020-01 | 3       |

- 69 630 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *L-serine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *L-serine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 100           | 0              | 146 629       |
| <b>Type C</b> | 0              | 3             | 0              | 69 630        |

The substance/substance group *L-serine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8817 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22289     | 22289               | 0.00                         | 70.60                           |
| 22668     | 22289               | 5.52                         | 62.11                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **L-threonine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20734-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

L-threonine; Threoninum

### Special notes

When selecting the *L-threonine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *L-threonine*:

| Supplier | Substance   | Batch      | Sample ID | Spectra | Certificate |
|----------|-------------|------------|-----------|---------|-------------|
| Fagron   | L-threonine | 12H02-N03  | 20734     | 40      | 1402580     |
| Euro OTC | L-threonine | 1210027-01 | 21033     | 40      | 1403152     |
| Euro OTC | L-threonine | 1601031    | 22378     | 40      | 20160225*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *L-threonine*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 5 reference samples from the substance/substance group *L-threonine*.

| Supplier    | Substance   | Batch      | Sample ID | Spectra |
|-------------|-------------|------------|-----------|---------|
| Pharmorgana | L-threonine | 1000110839 | 20410     | 40      |
| Euro OTC    | L-threonine | 1210027-01 | 22319     | 60      |
| Euro OTC    | L-threonine | 1606019    | 22679     | 40      |
| Euro OTC    | L-threonine | 1609014    | 22792     | 40      |
| Euro OTC    | L-threonine | 1703035    | 23158     | 40      |

- 146 509 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 7 spectra from 2 *Apo-Ident* customers from 5 batches from the substance/substance group *L-threonine*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier    | Substance   | Batch      | Spectra |
|-------------|-------------|------------|---------|
| Euro OTC    | L-threonine | 1210027-02 | 2       |
| Pharmorgana | L-threonine | 100110839  | 1       |
| Euro OTC    | L-threonine | 1210027-01 | 2       |
| Euro OTC    | L-threonine | 1111015-01 | 1       |
| Fargon      | L-threonine | 2114720407 | 1       |

- 69 626 spectra from 414 *Apo-Ident* customers from a total of 23 796 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *L-threonine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *L-threonine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 220           | 0              | 146 509       |
| <b>Type C</b> | 0              | 7             | 0              | 69 626        |

The substance/substance group *L-threonine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.2727 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20734     | 20734               | 0.00                         | 63.28                           |
| 21033     | 21033               | 0.00                         | 61.78                           |
| 22378     | 22378               | 0.00                         | 66.04                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **L-tryptophan**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20336-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

L-tryptophan; Tryptophanum

### Special notes

When selecting the *L-tryptophan* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *L-tryptophan*:

| Supplier | Substance    | Batch            | Sample ID | Spectra | Certificate        |
|----------|--------------|------------------|-----------|---------|--------------------|
| Fagron   | L-tryptophan | 14B05-B32-293485 | 21784     | 40      | AR-15-FG-009473-01 |
| Euro OTC | L-tryptophan | 1506003          | 21866     | 40      | 20150630*          |
| Euro OTC | L-tryptophan | 1506003          | 21871     | 40      | 20150630*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group L-tryotophan. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 7 reference samples from the substance/substance group L-tryotophan.

| Supplier | Substance    | Batch            | Sample ID          | Spectra |
|----------|--------------|------------------|--------------------|---------|
| Fagron   | L-tryotophan | 11G25-N02        | 20336              | 40      |
| Fagron   | L-tryotophan | 9L28-N03         | 20369              | 40      |
| Fagron   | L-tryotophan | 10I28-806        | 20387              | 40      |
| Fagron   | L-tryotophan | 14B05-B32-293485 | 21784 <sup>†</sup> | 20      |
| Euro OTC | L-tryotophan | 1506003          | 21866 <sup>†</sup> | 20      |
| Euro OTC | L-tryotophan | 1506003          | 21871 <sup>†</sup> | 20      |
| Fagron   | L-tryotophan | 16E11-B03-322919 | 23195              | 40      |

- 146 509 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 23 spectra from 7 *Apo-Ident* customers from 12 batches from the substance/substance group L-tryotophan.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier    | Substance    | Batch       | Spectra |
|-------------|--------------|-------------|---------|
| Pharmorgana | L-tryptophan | 1000140147  | 1       |
| Fagron      | L-tryptophan | 13J10-N03   | 2       |
| Caelo       | L-tryptophan | 131046      | 1       |
| Fagron      | L-tryptophan | 11G25-N02   | 3       |
| Fagron      | L-tryptophan | 11D15-N04   | 1       |
| Fagron      | L-tryptophan | Ch12K02-N05 | 1       |
| Euro OTC    | L-tryptophan | 1111044-01  | 1       |
| euroct/gehe | L-tryptophan | 1212010-01  | 5       |
| Euro OTC    | L-tryptophan | 1212010-01  | 1       |
| Euro OTC    | L-tryptophan | 1302021-01  | 1       |
| Euro OTC    | L-tryptophan | 1404027-01  | 2       |
| Euro OTC    | L-tryptophan | 1307004-01  | 3       |
| Fagron      | L-tryptophan | 12B14-N15   | 1       |

- 69 610 spectra from 414 *Apo-Ident* customers from a total of 23 789 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *L-tryptophan* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *L-tryptophan* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 215           | 5              | 146 509       |
| <b>Type C</b> | 0              | 23            | 0              | 69 610        |

The substance/substance group *L-tryptophan* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 97.7273 % (> 96.3636 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 73.9130 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21784     | 21784               | 0.00                         | 61.68                           |
| 21866     | 21866               | 0.00                         | 60.10                           |
| 21871     | 21871               | 0.00                         | 60.59                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Lysine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20385-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Lysine hydrochloride; Lysine HCl; Lysini hydrochloridum; Lysini hydrochloridum Inf

### Special notes

When selecting the *Lysine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Lysine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Lysine hydrochlo... | 15B09-B06-304170 | 21963     | 40      | 20150220           |
| Fagron   | Lysine hydrochlo... | 14H20-B03-301894 | 21983     | 40      | AR-16-FG-005856-01 |
| Euro OTC | Lysine hydrochlo... | 1708009          | 23698     | 40      | 20170922*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Lysine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 7 reference samples from the substance/substance group *Lysine hydrochloride*.

| Supplier | Substance            | Batch            | Sample ID          | Spectra |
|----------|----------------------|------------------|--------------------|---------|
| Euro OTC | Lysine hydrochloride | L1103041-01      | 20385              | 40      |
| Dr. Behr | Lysine hydrochloride | P-07014932       | 20402              | 40      |
| Fagron   | Lysine hydrochloride | 12B14-N08        | 20735              | 40      |
| Fagron   | Lysine hydrochloride | 15B09-B06-304170 | 21963 <sup>†</sup> | 20      |
| Fagron   | Lysine hydrochloride | 14H20-B03-301894 | 21983 <sup>†</sup> | 20      |
| Euro OTC | Lysine hydrochloride | 1603011          | 22527              | 40      |
| Euro OTC | Lysine hydrochloride | 1611021          | 22865              | 40      |

- 146 489 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 10 spectra from 4 *Apo-Ident* customers from 5 batches from the substance/substance group *Lysine hydrochloride*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance            | Batch            | Spectra |
|----------|----------------------|------------------|---------|
| Euro OTC | Lysine hydrochloride | L1209002-1       | 1       |
| Euro OTC | Lysine hydrochloride | L1304015-01      | 5       |
| Euro OTC | Lysine hydrochloride | L1205030-01      | 1       |
| Fagron   | Lysine hydrochloride | 14H20-B03-301894 | 1       |
| Fagron   | Lysine hydrochloride | 2167210405       | 1       |
| AHD      | Lysine hydrochloride | L1304015-01      | 1       |

- 69 623 spectra from 414 *Apo-Ident* customers from a total of 23 796 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Lysine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Lysine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 120           | 120            | 146 489       |
| <b>Type C</b> | 0              | 9             | 1              | 69 623        |

The substance/substance group *Lysine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 50.0000 % (> 48.7500 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21963     | 21983               | 3.85                         | 56.07                           |
| 21983     | 21983               | 0.00                         | 59.65                           |
| 23698     | 23698               | 0.00                         | 62.05                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Macrogol 1500**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20112-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Macrogol 1500; Macrogolum 1500; Polyäthylenglycolum 1500

### Special notes

When selecting the *Macrogol 1500* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Macrogol 1500*:

| Supplier | Substance     | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------|----------|-----------|---------|-------------|
| Caelo    | Macrogol 1500 | 12324607 | 20977     | 40      | 1403323     |
| Euro OTC | Macrogol 1500 | 1508002  | 21948     | 40      | 20150810*   |
| Euro OTC | Macrogol 1500 | 1604005  | 22544     | 40      | 20160512*   |
| Caelo    | Macrogol 1500 | 17120001 | 23241     | 40      | 20170519    |
| Caelo    | Macrogol 1500 | 171200   | 23291     | 40      | 20170519*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Macrogol 1500*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 210 spectra of 5 reference samples from the substance/substance group *Macrogol 1500*.

| Supplier | Substance     | Batch    | Sample ID          | Spectra |
|----------|---------------|----------|--------------------|---------|
| Caelo    | Macrogol 1500 | 10037704 | 20112              | 70      |
| Euro OTC | Macrogol 1500 | 1508002  | 21948 <sup>†</sup> | 20      |
| Euro OTC | Macrogol 1500 | 1705004  | 23423              | 40      |
| Euro OTC | Macrogol 1500 | 1705036  | 23440              | 40      |
| Caelo    | Macrogol 1500 | 172221   | 23625              | 40      |

- 146 519 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 42 spectra from 18 *Apo-Ident* customers from 20 batches from the substance/substance group *Macrogol 1500*.

| Supplier         | Substance     | Batch      | Spectra |
|------------------|---------------|------------|---------|
| Euro OTC         | Macrogol 1500 | 1304023-01 | 7       |
| Caelo            | Macrogol 1500 | 13140902   | 2       |
| Euro OTC         | Macrogol 1500 | 1406004-01 | 2       |
| Caelo            | Macrogol 1500 | 14072412   | 1       |
| Gehe             | Macrogol 1500 | 14072409   | 1       |
| Phönix           | Macrogol 1500 | 14072402   | 1       |
| Euro OTC         | Macrogol 1500 | 1503026-01 | 4       |
| Caelo            | Macrogol 1500 | 15120007   | 1       |
| Caelo            | Macrogol 1500 | 11056504   | 1       |
| Caelo            | Macrogol 1500 | 10105905   | 1       |
| Caelo            | Macrogol 1500 | 10105901   | 1       |
| Caelo            | Macrogol 1500 | 15413111   | 1       |
| Caelo            | Macrogol 1500 | 11071309   | 1       |
| Euro OTC         | Macrogol 1500 | 1206005-01 | 7       |
| Caelo            | Macrogol 1500 | 12109409   | 2       |
| Anzag 21.06.2013 | Macrogol 1500 | 12324610   | 1       |
| Caelo            | Macrogol 1500 | 13140901   | 1       |
| Caelo            | Macrogol 1500 | 13140906   | 2       |
| Euro OTC         | Macrogol 1500 | 1103017-02 | 4       |
| ACM / Herba      | Macrogol 1500 | KN-0826/10 | 1       |

- 69 591 spectra from 414 *Apo-Ident* customers from a total of 23 781 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Macrogol 1500* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Macrogol 1500* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 180           | 30             | 146 519       |
| <b>Type C</b> | 0              | 40            | 2              | 69 591        |

The substance/substance group *Macrogol 1500* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 85.7143 % (> 84.2857 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 95.2381 % (> 88.0952 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several

new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20977     | 20977               | 0.00                         | 28.93                           |
| 21948     | 21948               | 0.00                         | 47.57                           |
| 22544     | 22544               | 0.00                         | 43.01                           |
| 23241     | 23291               | 6.28                         | 30.82                           |
| 23291     | 23291               | 0.00                         | 32.22                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Macrogol 4000**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20690-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Macrogol 4000; Macrogolum 4000; Polyäthylenglykolum 4000

### Special notes

When selecting the *Macrogol 4000* substance/substance group, the following information is displayed to the user:

- Advice for the distinction from Macrogol 6000: Macrogol 4000 cannot be certainly distinct from Macrogol 6000, which is however currently not deliverable in Germany.

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Macrogol 4000*:

| Supplier | Substance     | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------|----------|-----------|---------|-------------|
| Caelo    | Macrogol 4000 | 12074116 | 20690     | 40      | 1401164     |
| Caelo    | Macrogol 4000 | 12318019 | 20975     | 40      | 1403322     |
| Caelo    | Macrogol 4000 | 12361502 | 21065     | 40      | 20130107    |
| Caelo    | Macrogol 4000 | 13356616 | 21357     | 40      | 20131107    |

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| Supplier | Substance     | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------|------------------|-----------|---------|--------------------|
| Euro OTC | Macrogol 4000 | 1507004          | 21841     | 40      | 0000010550         |
| Fagron   | Macrogol 4000 | 15B13-B04-305461 | 21886     | 40      | AR-16-FG-004020-01 |
| Euro OTC | Macrogol 4000 | 1508031          | 21903     | 40      | 20150914*          |
| Euro OTC | Macrogol 4000 | 1605012          | 22567     | 40      | 20160606*          |
| Euro OTC | Macrogol 4000 | 1605025          | 22570     | 40      | 20160603*          |
| Fagron   | Macrogol 4000 | 16F10-B04-325645 | 23021     | 40      | 20160822           |
| Euro OTC | Macrogol 4000 | 1702003          | 23174     | 40      | 20170301*          |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 440 spectra of 11 reference samples from the substance/substance group *Macrogol 4000*. These samples are listed above in the [calibration samples](#) section.
- 70946 spectra from a total of 1541 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 510 spectra of 14 reference samples from the substance/substance group *Macrogol 4000*.

| Supplier | Substance     | Batch            | Sample ID          | Spectra |
|----------|---------------|------------------|--------------------|---------|
| Caelo    | Macrogol 4000 | 10059103         | 20114              | 70      |
| Fagron   | Macrogol 4000 | 10L02-N05        | 20172              | 30      |
| Fagron   | Macrogol 4000 | 10H03-N03        | 20173              | 30      |
| Caelo    | Macrogol 4000 | 11172433         | 20692              | 40      |
| Euro OTC | Macrogol 4000 | 1507004          | 21841 <sup>†</sup> | 20      |
| Fagron   | Macrogol 4000 | 15B13-B04-305461 | 21886 <sup>†</sup> | 20      |
| Euro OTC | Macrogol 4000 | 1508031          | 21903 <sup>†</sup> | 20      |
| Euro OTC | Macrogol 4000 | 1609018          | 22791              | 40      |
| Euro OTC | Macrogol 4000 | 1701007          | 22983              | 40      |
| Caelo    | Macrogol 4000 | 170686           | 23280              | 40      |
| Caelo    | Macrogol 4000 | 171190           | 23282              | 40      |
| Euro OTC | Macrogol 4000 | 1705019          | 23433              | 40      |
| Euro OTC | Macrogol 4000 | 1707026          | 23537              | 40      |
| Caelo    | Macrogol 4000 | 172081           | 23657              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

- 146 219 spectra from a total of 3180 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 431 spectra from 121 *Apo-Ident* customers from 200 batches from the substance/substance group *Macrogol 4000*.

| Supplier         | Substance     | Batch      | Spectra |
|------------------|---------------|------------|---------|
| Fagron           | Macrogol 4000 | 2022015A   | 1       |
| Fagron           | Macrogol 4000 | 3032014B   | 1       |
| Fagron           | Macrogol 4000 | 505201C    | 1       |
| Fagron           | Macrogol 4000 | 8012015A   | 1       |
| Fagron           | Macrogol 4000 | 8062015B   | 1       |
| Fagron           | Macrogol 4000 | 8062015C   | 1       |
| Fagron           | Macrogol 4000 | 10022015A  | 1       |
| Fagron           | Macrogol 4000 | 914I-02103 | 1       |
| Fagron           | Macrogol 4000 | 10022015B  | 1       |
| Euro OTC         | Macrogol 4000 | 1005011-01 | 1       |
| Henry Lamotte    | Macrogol 4000 | 1213test   | 1       |
| Caelo            | Macrogol 4000 | 1180513    | 1       |
| Caelo            | Macrogol 4000 | 123Test    | 1       |
| Caelo            | Macrogol 4000 | 1234       | 1       |
| Fagron           | Macrogol 4000 | 123Test    | 1       |
| Euro OTC         | Macrogol 4000 | 1305020-02 | 3       |
| Euro OTC         | Macrogol 4000 | 130502002  | 1       |
| Caelo            | Macrogol 4000 | 13081501   | 1       |
| Caelo            | Macrogol 4000 | 13136011   | 4       |
| Caelo            | Macrogol 4000 | 13136016   | 2       |
| Caelo            | Macrogol 4000 | 13335102   | 2       |
| Caelo            | Macrogol 4000 | 13335107   | 1       |
| Caelo            | Macrogol 4000 | 13335120   | 1       |
| Caelo            | Macrogol 4000 | 13356601   | 5       |
| GEHE 06.05.2014  | Macrogol 4000 | 13356608   | 2       |
| Caelo            | Macrogol 4000 | 13356611   | 4       |
| Caelo            | Macrogol 4000 | 13356609   | 4       |
| ANZAG 15.05.2014 | Macrogol 4000 | 13356616   | 1       |
| Caelo            | Macrogol 4000 | 13356616   | 2       |
| Caelo            | Macrogol 4000 | 13356617   | 8       |
| Caelo            | Macrogol 4000 | 13356621   | 1       |
| Fagron           | Macrogol 4000 | 13G19-N08  | 3       |
| Fagron           | Macrogol 4000 | 13I17-N03  | 1       |
| Caelo            | Macrogol 4000 | 1401708    | 1       |
| Caelo            | Macrogol 4000 | 14061705   | 10      |
| Caelo            | Macrogol 4000 | 14061707   | 6       |
| Caelo            | Macrogol 4000 | 14061708   | 13      |
| Fagron           | Macrogol 4000 | 14061710   | 1       |
| Caelo            | Macrogol 4000 | 14061712   | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| <b>Supplier</b>          | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|--------------------------|------------------|------------------|----------------|
| Caelo                    | Macrogol 4000    | 14061713         | 1              |
| Euro OTC                 | Macrogol 4000    | 140701001        | 1              |
| Caelo                    | Macrogol 4000    | 14180503         | 1              |
| Caelo                    | Macrogol 4000    | 14180508         | 2              |
| Caelo                    | Macrogol 4000    | 14180511         | 4              |
| Caelo                    | Macrogol 4000    | 14180512         | 1              |
| Caelo                    | Macrogol 4000    | 14180513         | 1              |
| Caelo                    | Macrogol 4000    | 14180520         | 3              |
| Caelo                    | Macrogol 4000    | 14180524         | 1              |
| Caelo                    | Macrogol 4000    | 14180522         | 1              |
| Caesar & Loretz GmbH     | Macrogol 4000    | 14180520         | 1              |
| Caelo                    | Macrogol 4000    | 14180525         | 5              |
| Caelo                    | Macrogol 4000    | 1418521          | 1              |
| Caelo                    | Macrogol 4000    | 14196013         | 1              |
| Caesar&Loretz GmbH/Anzag | Macrogol 4000    | 14196017         | 1              |
| Caelo                    | Macrogol 4000    | 14352606         | 4              |
| Caelo                    | Macrogol 4000    | 14352607         | 2              |
| Caelo                    | Macrogol 4000    | 14352608         | 1              |
| Caelo                    | Macrogol 4000    | 14352611         | 1              |
| Fagron                   | Macrogol 4000    | 14352612         | 2              |
| Caelo                    | Macrogol 4000    | 14352612         | 1              |
| Caelo                    | Macrogol 4000    | 14352613         | 2              |
| Caelo                    | Macrogol 4000    | 14352618         | 2              |
| Caelo                    | Macrogol 4000    | 14352614         | 1              |
| Fagron                   | Macrogol 4000    | 14A03B01         | 1              |
| Fagron                   | Macrogol 4000    | 14A03-B01        | 1              |
| Fagron                   | Macrogol 4000    | 14A03-B01-289602 | 3              |
| Fagron                   | Macrogol 4000    | 14A03-B01-289605 | 3              |
| Fagron                   | Macrogol 4000    | 14A03-B01-289603 | 1              |
| Fagron                   | Macrogol 4000    | 14B28-B03        | 1              |
| Fagron                   | Macrogol 4000    | 14D14-B06        | 1              |
| Fagron                   | Macrogol 4000    | 14D14-B06-293453 | 3              |
| Fagron                   | Macrogol 4000    | 14D14-B06-293454 | 1              |
| Fagron                   | Macrogol 4000    | 14G15-B07-295634 | 1              |
| Fagron                   | Macrogol 4000    | 14G15-B07-295632 | 1              |
| Fagron                   | Macrogol 4000    | 14K03-b07-300522 | 1              |
| Fagron                   | Macrogol 4000    | 14K03-B07-300522 | 2              |
| Fagron                   | Macrogol 4000    | 14L12-B06-301991 | 1              |
| Fagron                   | Macrogol 4000    | 15/29-B01-318038 | 2              |
| Euro OTC                 | Macrogol 4000    | 1508031-01       | 1              |
| Euro OTC                 | Macrogol 4000    | 1507004-01       | 1              |
| Euro OTC                 | Macrogol 4000    | 1508031-02       | 1              |
| Caelo                    | Macrogol 4000    | 1508031-02       | 1              |
| Fagron                   | Macrogol 4000    | 15092014A        | 1              |
| Caelo                    | Macrogol 4000    | 15159502         | 1              |
| Caelo                    | Macrogol 4000    | 15159504         | 2              |
| Caelo                    | Macrogol 4000    | 15159514         | 4              |
| Caelo                    | Macrogol 4000    | 15159505         | 2              |
| Caelo                    | Macrogol 4000    | 15159506         | 1              |
| Caelo                    | Macrogol 4000    | 15159515         | 3              |
| Euro OTC                 | Macrogol 4000    | 15159515         | 1              |
| Caelo                    | Macrogol 4000    | 15159516         | 2              |
| Caelo                    | Macrogol 4000    | 15225001         | 1              |
| Caelo                    | Macrogol 4000    | 15225003         | 4              |
| Caelo                    | Macrogol 4000    | 15225013         | 1              |
| Caelo                    | Macrogol 4000    | 15335001         | 5              |
| Caelo                    | Macrogol 4000    | 15335003         | 11             |
| Caelo                    | Macrogol 4000    | 15335007         | 3              |
| Caelo                    | Macrogol 4000    | 1535004          | 1              |
| Caelo                    | Macrogol 4000    | 15376503         | 2              |

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| <b>Supplier</b>    | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|--------------------|------------------|------------------|----------------|
| Caelo              | Macrolog 4000    | 15406301         | 5              |
| Caelo              | Macrolog 4000    | 15406302         | 2              |
| Caelo              | Macrolog 4000    | 15406303         | 4              |
| Fagron             | Macrolog 4000    | 15A08-B03        | 1              |
| Caelo              | Macrolog 4000    | 15406306         | 1              |
| Fagron             | Macrolog 4000    | 15A08-B03-302761 | 1              |
| Fagron             | Macrolog 4000    | 15A08-B03-302762 | 3              |
| Fagron             | Macrolog 4000    | 15B13-B04-305461 | 2              |
| Fagron             | Macrolog 4000    | 15H10-B04-314037 | 2              |
| Fagron             | Macrolog 4000    | 15A08B03302762   | 1              |
| Fagron             | Macrolog 4000    | 15H10-B04-31407  | 1              |
| Fagron             | Macrolog 4000    | 15I29-B01-318038 | 1              |
| Caelo              | Macrolog 4000    | 16023903         | 3              |
| Caelo              | Macrolog 4000    | 16023904         | 2              |
| Phoenix            | Macrolog 4000    | 16023905         | 1              |
| Rondell Apotheke   | Macrolog 4000    | 16023905         | 1              |
| Caelo              | Macrolog 4000    | 16152001         | 5              |
| Fagron             | Macrolog 4000    | 160514a          | 1              |
| Caelo              | Macrolog 4000    | 16152003         | 3              |
| Caelo              | Macrolog 4000    | 16267305         | 4              |
| Caelo              | Macrolog 4000    | 16267307         | 5              |
| Caelo              | Macrolog 4000    | 16267308         | 3              |
| Caelo              | Macrolog 4000    | 16267311         | 2              |
| Caelo              | Macrolog 4000    | 16308902         | 5              |
| Caelo              | Macrolog 4000    | 16308904         | 6              |
| Caelo              | Macrolog 4000    | 16308905         | 1              |
| Caelo              | Macrolog 4000    | 16308907         | 3              |
| VDL                | Macrolog 4000    | 16308906         | 1              |
| Fagron             | Macrolog 4000    | 16A20-B15-320652 | 6              |
| Fagron             | Macrolog 4000    | 16A20-B15-320060 | 1              |
| Fagron             | Macrolog 4000    | 16a20-b15-320652 | 8              |
| Caelo              | Macrolog 4000    | 17035604         | 1              |
| Fagron             | Macrolog 4000    | 18082014C        | 1              |
| Fagron             | Macrolog 4000    | 20092014A        | 1              |
| Fagron             | Macrolog 4000    | 21052015A        | 1              |
| Fagron             | Macrolog 4000    | 22062015A        | 1              |
| Fagron             | Macrolog 4000    | 22122014A        | 1              |
| Fagron             | Macrolog 4000    | 25082014A        | 1              |
| Caelo              | Macrolog 4000    | 23061505         | 1              |
| Fagron             | Macrolog 4000    | 2215I-02103      | 1              |
| Fagron             | Macrolog 4000    | 26052014A        | 1              |
| Fagron             | Macrolog 4000    | 28052014B        | 1              |
| Fagron             | Macrolog 4000    | 290714c          | 1              |
| Fagron             | Macrolog 4000    | 30092014B        | 1              |
| Caelo              | Macrolog 4000    | 4123585          | 1              |
| Fagron             | Macrolog 4000    | 2122013b         | 1              |
| Fagron             | Macrolog 4000    | 2122013a         | 1              |
| Caelo              | Macrolog 4000    |                  | 1              |
| Facron             | Macrolog 4000    | 7022014C         | 1              |
| Euro OTC           | Macrolog 4000    | 1010023-02       | 1              |
| Caelo              | Macrolog 4000    | 1010023-02       | 1              |
| Fagron             | Macrolog 4000    | 1112M-02103      | 1              |
| Caelo              | Macrolog 4000    | 11172303         | 1              |
| Phoenix 14.05.2012 | Macrolog 4000    | 11H01-N04        | 1              |
| Caelo              | Macrolog 4000    | 1172404          | 1              |
| Euro OTC           | Macrolog 4000    | 1202040-02       | 3              |
| Caelo              | Macrolog 4000    | 11I05-N11        | 1              |
| Caelo              | Macrolog 4000    | 12074109         | 4              |
| Caelo              | Macrolog 4000    | 12074102         | 1              |
| EuRho              | Macrolog 4000    | 1206009-01       | 1              |

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| <b>Supplier</b>     | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|---------------------|------------------|--------------|----------------|
| Caelo               | Macrogol 4000    | 12074114     | 2              |
| Caelo               | Macrogol 4000    | 12149103     | 1              |
| Caelo               | Macrogol 4000    | 12149108     | 1              |
| Caelo               | Macrogol 4000    | 12074116     | 3              |
| Caelo               | Macrogol 4000    | 12149113     | 2              |
| Caelo               | Macrogol 4000    | 12149115     | 2              |
| Gehe                | Macrogol 4000    | 1219-N13     | 1              |
| Caelo               | Macrogol 4000    | 12318011     | 2              |
| Caelo               | Macrogol 4000    | 12318019     | 2              |
| Caelo               | Macrogol 4000    | 12318027     | 1              |
| Noweda              | Macrogol 4000    | 12361502     | 2              |
| Caelo               | Macrogol 4000    | 12361506     | 10             |
| Phönix Gotha        | Macrogol 4000    | 12361502     | 1              |
| Caelo               | Macrogol 4000    | 12361502     | 2              |
| Noweda              | Macrogol 4000    | 12361512     | 1              |
| Caelo               | Macrogol 4000    | 12361512     | 2              |
| Alliance Healthcare | Macrogol 4000    | 12361512     | 1              |
| Caelo               | Macrogol 4000    | 12361513     | 3              |
| Caelo               | Macrogol 4000    | 12361518     | 7              |
| Fagron              | Macrogol 4000    | 12A12-N07    | 2              |
| Fagron              | Macrogol 4000    | 12C29-N15    | 1              |
| Fagron              | Macrogol 4000    | 12F13-N01    | 2              |
| Fagron              | Macrogol 4000    | 12F29-N01    | 2              |
| Fagron              | Macrogol 4000    | 12F29-N01    | 1              |
| Fagron              | Macrogol 4000    | 12I20-N03    | 1              |
| Fagron              | Macrogol 4000    | 12I20-n03    | 1              |
| Fagron              | Macrogol 4000    | 12L10-N06    | 2              |
| Caelo               | Macrogol 4000    | 13136001     | 4              |
| DIV GH              | Macrogol 4000    | 13/12        | 1              |
| Caelo               | Macrogol 4000    | 13136003     | 3              |
| Noweda              | Macrogol 4000    | 13136003     | 1              |
| Caelo               | Macrogol 4000    | 13136009     | 3              |
| Caelo               | Macrogol 4000    | 13136010     | 1              |
| Bombastus           | Macrogol 4000    | 13136016     | 1              |
| Caelo               | Macrogol 4000    | 1316003      | 1              |
| Caelo               | Macrogol 4000    | 13356602     | 4              |
| Fagron              | Macrogol 4000    | 13B20-N01    | 2              |
| Sanacorp            | Macrogol 4000    | 13B20-N01    | 1              |
| Fagron              | Macrogol 4000    | 13B20N01     | 1              |
| Fagron              | Macrogol 4000    | 13F12-N09    | 1              |
| Fagron              | Macrogol 4000    | 13F12N09     | 1              |
| Hedinger            | Macrogol 4000    | 13G19-N08    | 1              |
| Sanacorp            | Macrogol 4000    | 14061707     | 1              |
| Fagron              | Macrogol 4000    | 17012014A    | 1              |
| Fagron              | Macrogol 4000    | 20122013C    | 1              |
| Fagron              | Macrogol 4000    | 16102013A    | 1              |
| Fagron              | Macrogol 4000    | 26082013A    | 1              |
| Fagron              | Macrogol 4000    | 280913C      | 2              |
| Caelo               | Macrogol 4000    | IntCh217002  | 1              |
| Caelo               | Macrogol 4000    | 16023905     | 1              |
| Fagron              | Macrogol 4000    | 3114I-02103  | 1              |
| Caelo               | Macrogol 4000    | 11172308     | 1              |
| Caelo               | Macrogol 4000    | 11172319     | 1              |
| Caelo               | Macrogol 4000    | 3940608      | 1              |
| Gutenberg-Apotheke  | Macrogol 4000    | 13356609     | 1              |
| Caelo               | Macrogol 4000    | 14180526     | 1              |
| Caelo               | Macrogol 4000    | 14196007     | 1              |
| Phoenix             | Macrogol 4000    | 12258901     | 1              |
| Caelo               | Macrogol 4000    | 13335106     | 1              |
| Fagron              | Macrogol 4000    | 13136010     | 1              |

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| Supplier        | Substance     | Batch    | Spectra |
|-----------------|---------------|----------|---------|
| Ichthyol/Phönix | Macrogol 4000 | 13356602 | 3       |

- 69 202 spectra from 414 *Apo-Ident* customers from a total of 23 604 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Macrogol 4000* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Macrogol 4000* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 440           | 0              | 70 946        |
| <b>Type B</b> | 0              | 496           | 14             | 146 019       |
| <b>Type C</b> | 0              | 430           | 1              | 69 199        |

The substance/substance group *Macrogol 4000* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.6364 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 97.2549 % (> 96.6667 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8817 %) | 99.7680 % (> 99.0719 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20690     | 20690               | 0.00                         | 41.50                           |
| 20975     | 20975               | 0.00                         | 41.25                           |
| 21065     | 20690               | 6.78                         | 40.13                           |

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| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21357            | 21886                      | 6.25                                | 37.59                                  |
| 21841            | 21841                      | 0.00                                | 35.17                                  |
| 21886            | 21886                      | 0.00                                | 42.63                                  |
| 21903            | 21903                      | 0.00                                | 51.00                                  |
| 22567            | 22567                      | 0.00                                | 33.73                                  |
| 22570            | 22570                      | 0.00                                | 44.97                                  |
| 23021            | 21886                      | 4.87                                | 42.22                                  |
| 23174            | 23174                      | 0.00                                | 53.59                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Magnesium (hydrogen) citrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20016-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Magnesium (hydrogen) citrate; Magnesii hydrogenocitras hydricus; Magnesii hydrogenocitricum

### Special notes

When selecting the *Magnesium (hydrogen) citrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Magnesium (hydrogen) citrate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Magnesium (hydro... | 13389102 | 21445     | 40      | 20131205    |
| Euro OTC | Magnesium (hydro... | 1507010  | 21873     | 40      | 20150713*   |
| Euro OTC | Magnesium (hydro... | 1510033  | 22233     | 40      | 20151117*   |
| Euro OTC | Magnesium (hydro... | 1601005  | 22296     | 40      | 20160119*   |
| Euro OTC | Magnesium (hydro... | 1701003  | 22992     | 40      | 20170124*   |
| Caelo    | Magnesium (hydro... | 15415014 | 23240     | 40      | 20160105    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Magnesium (hydrogen) citrate*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 475 spectra of 13 reference samples from the substance/substance group *Magnesium (hydrogen) citrate*.

| Supplier         | Substance                    | Batch      | Sample ID          | Spectra |
|------------------|------------------------------|------------|--------------------|---------|
| Caelo            | Magnesium (hydrogen) citrate | 90396239   | 20016              | 75      |
| Caelo            | Magnesium (hydrogen) citrate | 11372907   | 20595              | 40      |
| Euro OTC         | Magnesium (hydrogen) citrate | 1110026-02 | 20599              | 40      |
| Dr. Paul Lohmann | Magnesium (hydrogen) citrate | 1048115    | 20615              | 40      |
| Caelo            | Magnesium (hydrogen) citrate | 13389102   | 21445 <sup>†</sup> | 20      |
| Euro OTC         | Magnesium (hydrogen) citrate | 1507010    | 21873 <sup>†</sup> | 20      |
| Euro OTC         | Magnesium (hydrogen) citrate | 1510033    | 22233 <sup>†</sup> | 20      |
| Euro OTC         | Magnesium (hydrogen) citrate | 1601005    | 22296 <sup>†</sup> | 20      |
| Euro OTC         | Magnesium (hydrogen) citrate | 1604002    | 22509              | 40      |
| Euro OTC         | Magnesium (hydrogen) citrate | 1608004    | 22796              | 40      |
| Euro OTC         | Magnesium (hydrogen) citrate | 1701004    | 22991              | 40      |
| Euro OTC         | Magnesium (hydrogen) citrate | 1705010    | 23380              | 40      |
| Euro OTC         | Magnesium (hydrogen) citrate | 1705009    | 23382              | 40      |

- 146 254 spectra from a total of 3181 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B*

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 451 spectra from 133 *Apo-Ident* customers from 162 batches from the substance/substance group *Magnesium (hydrogen) citrate*.

| Supplier                     | Substance                    | Batch       | Spectra |
|------------------------------|------------------------------|-------------|---------|
| Caelo                        | Magnesium (hydrogen) citrate | 15296709    | 5       |
| Caelo                        | Magnesium (hydrogen) citrate | 14265516    | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 15296801    | 4       |
| Caelo                        | Magnesium (hydrogen) citrate | 15415005    | 2       |
| Caelo                        | Magnesium (hydrogen) citrate | 15415010    | 5       |
| Euro OTC                     | Magnesium (hydrogen) citrate | 1604002-01  | 22      |
|                              | Magnesium (hydrogen) citrate | 1058172     | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 12175810    | 4       |
| Caelo                        | Magnesium (hydrogen) citrate | 12175807    | 3       |
| Fagron                       | Magnesium (hydrogen) citrate | 10D28-N22   | 1       |
| Euro OTC                     | Magnesium (hydrogen) citrate | 1110026-01  | 3       |
| GEHE                         | Magnesium (hydrogen) citrate | 1110026-02  | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 11193115    | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 1137199     | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 11372901    | 4       |
| Caelo                        | Magnesium (hydrogen) citrate | 11372902    | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 1137291     | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 12091303    | 1       |
| Fagron                       | Magnesium (hydrogen) citrate | 11H05-N07   | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 12175802    | 7       |
| Caelo                        | Magnesium (hydrogen) citrate | 12238002    | 7       |
| Caelo                        | Magnesium (hydrogen) citrate | 12238012    | 3       |
| Caelo                        | Magnesium (hydrogen) citrate | 12368003    | 9       |
| Caelo                        | Magnesium (hydrogen) citrate | 12368004    | 6       |
| Fagron                       | Magnesium (hydrogen) citrate | 12A30-N03   | 2       |
| Fagron                       | Magnesium (hydrogen) citrate | 12A30-N30   | 1       |
| Fagron                       | Magnesium (hydrogen) citrate | 12G10-N01   | 3       |
| Fagron                       | Magnesium (hydrogen) citrate | 12H28-N11   | 4       |
| Caelo                        | Magnesium (hydrogen) citrate | 26101203    | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 7011504     | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 1014E-01829 | 1       |
| Dr. Paul Lohmann             | Magnesium (hydrogen) citrate | 1077866     | 2       |
| Euro OTC                     | Magnesium (hydrogen) citrate | 1080144     | 1       |
| Euro OTC                     | Magnesium (hydrogen) citrate | 1306034-02  | 4       |
| Euro OTC                     | Magnesium (hydrogen) citrate | 1311003-01  | 13      |
| Caelo                        | Magnesium (hydrogen) citrate | 13233907    | 2       |
| Caelo                        | Magnesium (hydrogen) citrate | 13233910    | 4       |
| Caelo                        | Magnesium (hydrogen) citrate | 13233913    | 8       |
| Caelo                        | Magnesium (hydrogen) citrate | 13389111    | 5       |
| Alliance Health 05.09.2. ... | Magnesium (hydrogen) citrate | 13389111    | 2       |
| VDL;27.02.15                 | Magnesium (hydrogen) citrate | 13389111    | 1       |
| Euro OTC                     | Magnesium (hydrogen) citrate | 1404023-01  | 6       |
| Euro OTC                     | Magnesium (hydrogen) citrate | 1407048-01  | 4       |
| Euro OTC                     | Magnesium (hydrogen) citrate | 1407048-02  | 5       |
| Caelo                        | Magnesium (hydrogen) citrate | 14265503    | 10      |
| Caelo                        | Magnesium (hydrogen) citrate |             | 1       |
| Caelo                        | Magnesium (hydrogen) citrate | 14265517    | 1       |
| Nowed18.08.2015              | Magnesium (hydrogen) citrate | 14265521    | 1       |

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| Supplier                   | Substance                    | Batch            | Spectra |
|----------------------------|------------------------------|------------------|---------|
| Fagron                     | Magnesium (hydrogen) citrate | 14I12-B02-298854 | 1       |
| Fagron                     | Magnesium (hydrogen) citrate | 14K27-B03-305254 | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1507010-01       | 9       |
| Caelo                      | Magnesium (hydrogen) citrate | 15296701         | 6       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1510033-01       | 2       |
| Caelo                      | Magnesium (hydrogen) citrate | 15415001         | 2       |
| Caelo                      | Magnesium (hydrogen) citrate | 15415002         | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1601005-01       | 10      |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1604002-012x     | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1604002-02       | 5       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1608004-01       | 7       |
| Gehe/EuRho                 | Magnesium (hydrogen) citrate | 112E-01829       | 1       |
| Eu Rho                     | Magnesium (hydrogen) citrate | 110600401        | 1       |
| Dr. Paul Lohmann           | Magnesium (hydrogen) citrate | 1079474          | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1202034          | 1       |
| Phoenix 30.07.2012         | Magnesium (hydrogen) citrate | 1202034-01       | 1       |
| Eu Rho                     | Magnesium (hydrogen) citrate | 1202034-01       | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1202034-01       | 2       |
| EuRho/Phönix               | Magnesium (hydrogen) citrate | 1202034-02       | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1208006-01       | 6       |
| Gehe 18.06.2013            | Magnesium (hydrogen) citrate | 1208006-02       | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1211033-02       | 4       |
| Caelo                      | Magnesium (hydrogen) citrate | 12175801         | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 12175804         | 2       |
| Gehe                       | Magnesium (hydrogen) citrate | 12368014         | 1       |
| Fagron                     | Magnesium (hydrogen) citrate | 13233901         | 2       |
| Caelo                      | Magnesium (hydrogen) citrate | 133233907        | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 2368011          | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 14265520         | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | C6H6Mg07         | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate |                  | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 11372907         | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 315E-01829       | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 516Q-01829       | 1       |
| Heidelberger Chlorella/... | Magnesium (hydrogen) citrate | 10032            | 1       |
| Heide/Gehe                 | Magnesium (hydrogen) citrate | 1077866          | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1085730          | 2       |
| Caelo                      | Magnesium (hydrogen) citrate | 1311003-01       | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 13233906         | 10      |
| Caelo                      | Magnesium (hydrogen) citrate | 13389106         | 3       |
| Caelo                      | Magnesium (hydrogen) citrate | 13389107         | 3       |
| Caelo                      | Magnesium (hydrogen) citrate | 13389108         | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 13389110         | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 14265504         | 4       |
| Caelo                      | Magnesium (hydrogen) citrate | 14265505         | 2       |
| Caelo                      | Magnesium (hydrogen) citrate | 14265511         | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 14265513         | 2       |
| Caelo                      | Magnesium (hydrogen) citrate | 14265521         | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 14I12-B02-298854 | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1507010-02       | 4       |
| Caelo                      | Magnesium (hydrogen) citrate | 15296712         | 2       |
| Caelo                      | Magnesium (hydrogen) citrate | 15296802         | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 15415009         | 2       |
| Caelo                      | Magnesium (hydrogen) citrate | 1604002-01       | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 16E02-B03-321485 | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | 1701003-01       | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 17061401         | 1       |
| Caelo                      | Magnesium (hydrogen) citrate | 5415013          | 1       |
| Euro OTC                   | Magnesium (hydrogen) citrate | L15402018-01     | 1       |
| Heidelberger/Noweda        | Magnesium (hydrogen) citrate | 1070876-2        | 1       |

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| <b>Supplier</b>  | <b>Substance</b>             | <b>Batch</b>     | <b>Spectra</b> |
|------------------|------------------------------|------------------|----------------|
| Caelo            | Magnesium (hydrogen) citrate | 11021401         | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 11044103         | 2              |
| Gehe/EuRho       | Magnesium (hydrogen) citrate | 1208006-2        | 1              |
| Kehr             | Magnesium (hydrogen) citrate | 12080206-01      | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 12105421         | 1              |
| Euro OTC         | Magnesium (hydrogen) citrate | 1211033-01       | 5              |
| Anzag            | Magnesium (hydrogen) citrate | 12175802         | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 12238001         | 3              |
| Caelo            | Magnesium (hydrogen) citrate | 12238003         | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 12238004         | 4              |
| Maros/Phönix     | Magnesium (hydrogen) citrate | 12238004         | 2              |
| Caelo            | Magnesium (hydrogen) citrate | 12368002         | 5              |
| Caelo            | Magnesium (hydrogen) citrate | 12368005         | 3              |
| Caelo            | Magnesium (hydrogen) citrate | 12368011         | 7              |
| Caelo            | Magnesium (hydrogen) citrate | 12368014         | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 12368014         | 2              |
| Fagron           | Magnesium (hydrogen) citrate | 12h28-n03        | 1              |
| Fagron           | Magnesium (hydrogen) citrate | 12H28-N03        | 1              |
| Euro OTC         | Magnesium (hydrogen) citrate | 1306034-01       | 3              |
| Caelo            | Magnesium (hydrogen) citrate | 13194601         | 5              |
| Caelo            | Magnesium (hydrogen) citrate | 13233901         | 9              |
| Caelo            | Magnesium (hydrogen) citrate | 13233904         | 5              |
| Caelo            | Magnesium (hydrogen) citrate | 13233907         | 2              |
| Caelo            | Magnesium (hydrogen) citrate | 13233911         | 4              |
| Caelo            | Magnesium (hydrogen) citrate | 13389103         | 8              |
| Caelo            | Magnesium (hydrogen) citrate | 27111306         | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 80446188         | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 11061403         | 1              |
| EuRho/Phönix     | Magnesium (hydrogen) citrate | 1311003-01       | 1              |
| Euro OTC         | Magnesium (hydrogen) citrate | 1311003-02       | 1              |
| Phoenix 15.10.14 | Magnesium (hydrogen) citrate | 1311003-01       | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 133389111        | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 13389102         | 2              |
| AHD              | Magnesium (hydrogen) citrate | 13389103         | 1              |
| Sanacaorp        | Magnesium (hydrogen) citrate | 13389108         | 1              |
| Fagron           | Magnesium (hydrogen) citrate |                  | 1              |
| Fagron           | Magnesium (hydrogen) citrate | 13K11-B02-288161 | 1              |
| Ichthyol/Phönix  | Magnesium (hydrogen) citrate | 14/12-B02-298854 | 1              |
| Gehe Kassel      | Magnesium (hydrogen) citrate | 14/12-B02-298854 | 1              |
| Euro OTC         | Magnesium (hydrogen) citrate | 140704801        | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 14265514         | 1              |
| Fagron           | Magnesium (hydrogen) citrate | 14I12-B02        | 1              |
| Euro OTC         | Magnesium (hydrogen) citrate | 1501026-01       | 3              |
| Euro OTC         | Magnesium (hydrogen) citrate | 151003301        | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 15296702         | 2              |
| Caelo            | Magnesium (hydrogen) citrate | 15415003         | 3              |
| Euro OTC         | Magnesium (hydrogen) citrate | 160100501        | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 1601005-01       | 1              |
| Euro OTC         | Magnesium (hydrogen) citrate | 160800401        | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 16341708         | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 16341709         | 1              |
| Euro OTC         | Magnesium (hydrogen) citrate | 2114M1829        | 1              |
| Euro OTC         | Magnesium (hydrogen) citrate | Ch1404023-01     | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 6081301          | 1              |
| Euro OTC         | Magnesium (hydrogen) citrate | 1010003-01       | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 913M-01829       | 1              |
| Noweda           | Magnesium (hydrogen) citrate | 10163306         | 1              |
| Fagron           | Magnesium (hydrogen) citrate | 1056239          | 1              |
| Dr. Paul Lohmann | Magnesium (hydrogen) citrate | 1078434          | 1              |
| Caelo            | Magnesium (hydrogen) citrate | 11193104         | 1              |

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| Supplier         | Substance                    | Batch        | Spectra |
|------------------|------------------------------|--------------|---------|
| Caelo            | Magnesium (hydrogen) citrate | 121033-01    | 1       |
| Phoenix 19.03.13 | Magnesium (hydrogen) citrate | 1208006-01   | 1       |
| Phönix           | Magnesium (hydrogen) citrate | 1211033-01   | 1       |
| Post-Apotheke    | Magnesium (hydrogen) citrate | 1211033-01   | 1       |
| Phönix 07.10.13  | Magnesium (hydrogen) citrate | 12368011     | 1       |
| Caelo            | Magnesium (hydrogen) citrate | 12368017     | 2       |
| Eu Rho           | Magnesium (hydrogen) citrate | 1306034-01   | 1       |
| Euro OTC         | Magnesium (hydrogen) citrate | 130603402    | 1       |
|                  | Magnesium (hydrogen) citrate | 1311003-01   | 1       |
| Caelo            | Magnesium (hydrogen) citrate | 13194603     | 1       |
| Caelo            | Magnesium (hydrogen) citrate | 13233905     | 1       |
| Fagron           | Magnesium (hydrogen) citrate | 13B22-N03    | 1       |
| Fagron           | Magnesium (hydrogen) citrate | 13D30-N07    | 2       |
| Fagron           | Magnesium (hydrogen) citrate | 13G02-N04    | 2       |
| Euro OTC         | Magnesium (hydrogen) citrate | 140402301    | 1       |
| Caelo            | Magnesium (hydrogen) citrate | 16061203     | 1       |
| Caelo            | Magnesium (hydrogen) citrate | 19061316     | 1       |
| Caelo            | Magnesium (hydrogen) citrate | 411052-2-P   | 1       |
| Caelo            | Magnesium (hydrogen) citrate | 28131-01829  | 1       |
| Caelo            | Magnesium (hydrogen) citrate | 90396169     | 1       |
| Euro OTC         | Magnesium (hydrogen) citrate | Ch1211033-02 | 3       |

- 69 182 spectra from 414 *Apo-Ident* customers from a total of 23 642 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Magnesium (hydrogen) citrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Magnesium (hydrogen) citrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 465           | 10             | 146 254       |
| <b>Type C</b> | 0              | 433           | 18             | 69 182        |

The substance/substance group *Magnesium (hydrogen) citrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 97.8947 % (> 97.2632 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 96.0089 % (> 95.3437 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)



In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21445     | 22233               | 5.18                         | 37.04                           |
| 21873     | 21873               | 0.00                         | 38.84                           |
| 22233     | 22233               | 0.00                         | 38.67                           |
| 22296     | 22296               | 0.00                         | 39.04                           |
| 22992     | 22992               | 0.00                         | 39.26                           |
| 23240     | 21873               | 2.36                         | 39.04                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Magnesium aspartate dihydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21976-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Magnesium aspartate dihydrate; Magnesii aspartas dihydricus

### Special notes

When selecting the *Magnesium aspartate dihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Magnesium aspartate dihydrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Magnesium aspart... | 15I24-B89-313231 | 22343     | 40      | AR-16-FG-008660-03 |
| Fagron   | Magnesium aspart... | 15I24-B89-313231 | 22353     | 40      | 20151016           |
| Fagron   | Magnesium aspart... | 17C21-B05-333111 | 23221     | 40      | 20170412           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Magnesium aspartate dihydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 40 spectra of 2 reference samples from the substance/substance group *Magnesium aspartate dihydrate*.

| Supplier | Substance                     | Batch            | Sample ID          | Spectra |
|----------|-------------------------------|------------------|--------------------|---------|
| Fagron   | Magnesium aspartate dihydrate | 15I24-B89-313231 | 22343 <sup>†</sup> | 20      |
| Fagron   | Magnesium aspartate dihydrate | 15I24-B89-313231 | 22353 <sup>†</sup> | 20      |

- 146 689 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Magnesium aspartate dihydrate*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Magnesium aspartate dihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Magnesium aspartate dihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 40            | 0              | 146 689       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Magnesium aspartate dihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 85.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22343     | 22343               | 0.00                         | 35.46                           |
| 22353     | 22343               | 1.75                         | 35.42                           |
| 23221     | 22343               | 19.66                        | 42.99                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Magnesium citrate, anhydrous**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20616-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Magnesium citrate, anhydrous; Magnesii citras anhydricus; Magnesii citricum siccatum

### Special notes

When selecting the *Magnesium citrate, anhydrous* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Magnesium citrate, anhydrous*:

| Supplier | Substance           | Batch   | Sample ID | Spectra | Certificate        |
|----------|---------------------|---------|-----------|---------|--------------------|
| Euro OTC | Magnesium citrat... | 1501031 | 21794     | 40      | AR-15-FG-007845-01 |
| Euro OTC | Magnesium citrat... | 1506020 | 21829     | 40      | 0000010379         |
| Euro OTC | Magnesium citrat... | 1507019 | 21860     | 40      | 0000010617         |
| Euro OTC | Magnesium citrat... | 1511018 | 22225     | 40      | 20151130*          |
| Euro OTC | Magnesium citrat... | 1602028 | 22505     | 40      | 20160314*          |
| Euro OTC | Magnesium citrat... | 1706007 | 23549     | 40      | 20170720*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Magnesium citrate, anhydrous*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 7 reference samples from the substance/substance group *Magnesium citrate, anhydrous*.

| Supplier         | Substance                    | Batch   | Sample ID          | Spectra |
|------------------|------------------------------|---------|--------------------|---------|
| Dr. Paul Lohmann | Magnesium citrate, anhydrous | 1040331 | 20616              | 40      |
| Euro OTC         | Magnesium citrate, anhydrous | 1501031 | 21794 <sup>†</sup> | 20      |
| Euro OTC         | Magnesium citrate, anhydrous | 1506020 | 21829 <sup>†</sup> | 20      |
| Euro OTC         | Magnesium citrate, anhydrous | 1507019 | 21860 <sup>†</sup> | 20      |
| Euro OTC         | Magnesium citrate, anhydrous | 1511018 | 22225 <sup>†</sup> | 20      |
| Euro OTC         | Magnesium citrate, anhydrous | 1607006 | 22673              | 40      |
| Euro OTC         | Magnesium citrate, anhydrous | 1701018 | 22998              | 40      |

- 146 529 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Magnesium citrate, anhydrous*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Magnesium citrate, anhydrous* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Magnesium citrate, anhydrous* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 192           | 8              | 146 529       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Magnesium citrate, anhydrous* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 96.0000 % (> 94.5000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21794     | 21794               | 0.00                         | 36.60                           |
| 21829     | 21829               | 0.00                         | 24.53                           |
| 21860     | 21860               | 0.00                         | 17.22                           |
| 22225     | 22225               | 0.00                         | 28.77                           |
| 22505     | 22505               | 0.00                         | 48.91                           |
| 23549     | 23549               | 0.00                         | 40.44                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | Magnesium hydrogen aspartate tetrahydrate                       |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20812-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Magnesium hydrogen aspartate tetrahydrate; Magnesii aspartas tetrahydricus; Magnesii asparticum tetrahydricum

### Special notes

When selecting the *Magnesium hydrogen aspartate tetrahydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Magnesium hydrogen aspartate tetrahydrate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Euro OTC | Magnesium hydrog... | 1204014-01 | 20812     | 40      | 1404588     |
| Euro OTC | Magnesium hydrog... | 1306045-01 | 21749     | 40      | 20130708    |
| Euro OTC | Magnesium hydrog... | 1605031    | 22682     | 40      | 20160617*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Magnesium hydrogen aspartate tetrahydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 6 reference samples from the substance/substance group *Magnesium hydrogen aspartate tetrahydrate*.

| Supplier | Substance                       | Batch      | Sample ID          | Spectra |
|----------|---------------------------------|------------|--------------------|---------|
| Euro OTC | Magnesium hydrogen aspartate... | 1012021-01 | 20384              | 40      |
| Euro OTC | Magnesium hydrogen aspartate... | 1012021-01 | 20441              | 40      |
| Euro OTC | Magnesium hydrogen aspartate... | 1012021    | 20614              | 40      |
| Euro OTC | Magnesium hydrogen aspartate... | 1306045-01 | 21749 <sup>†</sup> | 20      |
| Euro OTC | Magnesium hydrogen aspartate... | 1707010    | 23552              | 40      |
| Euro OTC | Magnesium hydrogen aspartate... | 1707010    | 23608              | 40      |

- 146 509 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 4 spectra from 2 *Apo-Ident* customers from 4 batches from the substance/substance group *Magnesium hydrogen aspartate tetrahydrate*.

| Supplier | Substance                       | Batch      | Spectra |
|----------|---------------------------------|------------|---------|
| Euro OTC | Magnesium hydrogen aspartate... | 1504036-01 | 1       |
| Euro OTC | Magnesium hydrogen aspartate... | 1605031-01 | 1       |
| Euro OTC | Magnesium hydrogen aspartate... | 1012021-01 | 1       |
| Euro OTC | Magnesium hydrogen aspartate... | 1204014-01 | 1       |

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Magnesium hydrogen aspartate tetrahydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Magnesium hydrogen aspartate tetrahydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 180           | 40             | 146 509       |
| <b>Type C</b> | 0              | 3             | 1              | 69 629        |

The substance/substance group *Magnesium hydrogen aspartate tetrahydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 81.8182 % (> 80.4545 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20812     | 20812               | 0.00                         | 43.53                           |
| 21749     | 20812               | 4.45                         | 43.24                           |
| 22682     | 22682               | 0.00                         | 43.97                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Magnesium orotate dihydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20429-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Magnesium orotate dihydrate; Magnesii orotas dihydricus; Magnesii oroticum dihydricum

### Special notes

When selecting the *Magnesium orotate dihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Magnesium orotate dihydrate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Euro OTC | Magnesium orotat... | 1511021  | 22287     | 40      | 20151228*   |
| Caelo    | Magnesium orotat... | 162227   | 22638     | 40      | 20160809*   |
| Caelo    | Magnesium orotat... | 16222701 | 23236     | 40      | 20160809    |
| Euro OTC | Magnesium orotat... | 1707018  | 23615     | 40      | 20170907*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Magnesium orotate dihydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Magnesium orotate dihydrate*.

| Supplier    | Substance                   | Batch      | Sample ID          | Spectra |
|-------------|-----------------------------|------------|--------------------|---------|
| Pharmorgana | Magnesium orotate dihydrate | 1000135398 | 20429              | 40      |
| Euro OTC    | Magnesium orotate dihydrate | 1109034-01 | 20531              | 40      |
| Euro OTC    | Magnesium orotate dihydrate | 1511021    | 22287 <sup>†</sup> | 20      |
| Euro OTC    | Magnesium orotate dihydrate | 1608017    | 22784              | 40      |
| Caelo       | Magnesium orotate dihydrate | 172157     | 23661              | 40      |

- 146 549 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 34 spectra from 14 *Apo-Ident* customers from 19 batches from the substance/substance group *Magnesium orotate dihydrate*.

| Supplier             | Substance                   | Batch            | Spectra |
|----------------------|-----------------------------|------------------|---------|
| Fagron               | Magnesium orotate dihydrate | 12G05-N03        | 1       |
| Euro OTC             | Magnesium orotate dihydrate | 1305011-02       | 5       |
| Fagron               | Magnesium orotate dihydrate | 14/13-B05-305616 | 1       |
| Euro OTC             | Magnesium orotate dihydrate | 1407005-01       | 2       |
| Caelo                | Magnesium orotate dihydrate | 14093607         | 2       |
| Fagron               | Magnesium orotate dihydrate | 14E20-B05-296005 | 1       |
| Euro OTC             | Magnesium orotate dihydrate | 1511021-02       | 6       |
| Euro OTC             | Magnesium orotate dihydrate | 1504002-01       | 1       |
| Euro OTC             | Magnesium orotate dihydrate | 1608017-01       | 1       |
| Microsin Pharmorgana | Magnesium orotate dihydrate | ORM00213         | 1       |
| Microsin Pharmorgana | Magnesium orotate dihydrate | ORM02514         | 1       |
| Microsin Pharmorgana | Magnesium orotate dihydrate | ORM09114         | 1       |
| Euro OTC             | Magnesium orotate dihydrate | 8120             | 2       |
| Phoenix 22.03.13     | Magnesium orotate dihydrate | 1209029-01       | 1       |
| Fagron               | Magnesium orotate dihydrate | 1000060461       | 1       |
| Euro OTC             | Magnesium orotate dihydrate | 1209029-01       | 3       |
| Euro OTC             | Magnesium orotate dihydrate | 1305011-01       | 1       |
| Fagron               | Magnesium orotate dihydrate | 13H06-N07        | 1       |
| Euro OTC             | Magnesium orotate dihydrate | ORM00113         | 1       |
| Microsin Pharmorgana | Magnesium orotate dihydrate | ORM00213         | 1       |

- 69 599 spectra from 414 *Apo-Ident* customers from a total of 23 783 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Magnesium orotate dihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Magnesium orotate dihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 140           | 40             | 146 549       |
| <b>Type C</b> | 0              | 33            | 1              | 69 599        |

The substance/substance group *Magnesium orotate dihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 77.7778 % (> 76.1111 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 97.0588 % (> 88.2353 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22287     | 22287               | 0.00                         | 72.28                           |
| 22638     | 22638               | 0.00                         | 84.95                           |
| 23236     | 23615               | 9.13                         | 86.41                           |
| 23615     | 23615               | 0.00                         | 80.88                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Magnesium stearate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20707-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Magnesium stearate; Magnesii stearas; Magnesii stearinicum

### Special notes

When selecting the *Magnesium stearate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Magnesium stearate*:

| Supplier | Substance          | Batch      | Sample ID | Spectra | Certificate        |
|----------|--------------------|------------|-----------|---------|--------------------|
| Fagron   | Magnesium stearate | 12C29-N06  | 20707     | 110     | 20120418           |
| Fagron   | Magnesium stearate | 12D26-B03  | 21084     | 40      | 1407310            |
| Caelo    | Magnesium stearate | 13095536   | 21117     | 40      | 20130405           |
| Caelo    | Magnesium stearate | 14136929   | 21783     | 40      | AR-15-FG-012028-01 |
| Euro OTC | Magnesium stearate | 1502033-01 | 22817     | 40      | 20150317           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 270 spectra of 5 reference samples from the substance/substance group *Magnesium stearate*. These samples are listed above in the [calibration samples](#) section.
- 71 116 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Magnesium stearate*.

| Supplier | Substance          | Batch    | Sample ID          | Spectra |
|----------|--------------------|----------|--------------------|---------|
| Caelo    | Magnesium stearate | 14136929 | 21783 <sup>†</sup> | 20      |
| Caelo    | Magnesium stearate | 162066   | 22763              | 40      |
| Euro OTC | Magnesium stearate | 1608022  | 22821              | 40      |
| Euro OTC | Magnesium stearate | 1704002  | 23436              | 40      |

- 146 589 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 14 spectra from 10 *Apo-Ident* customers from 12 batches from the substance/substance group *Magnesium stearate*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance          | Batch            | Spectra |
|----------|--------------------|------------------|---------|
| Caelo    | Magnesium stearate | 15155001         | 2       |
| Euro OTC | Magnesium stearate | 914I-01834       | 1       |
| Noweda   | Magnesium stearate | 13D11-N08        | 1       |
| Euro OTC | Magnesium stearate | 315E-01834       | 1       |
| Euro OTC | Magnesium stearate | 1116E-01834      | 1       |
| Caelo    | Magnesium stearate | 13095536         | 1       |
| Fagron   | Magnesium stearate | 12D26-B03-289435 | 1       |
| Caelo    | Magnesium stearate | 13095515         | 1       |
| Caelo    | Magnesium stearate | 15305315         | 2       |
| Caelo    | Magnesium stearate | 15305307         | 1       |
| Caelo    | Magnesium stearate | 12040307         | 1       |
| Euro OTC | Magnesium stearate | 1912I-01834      | 1       |

- 69 619 spectra from 414 *Apo-Ident* customers from a total of 23 789 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Magnesium stearate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Magnesium stearate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 270           | 0              | 71 116        |
| <b>Type B</b> | 0              | 140           | 0              | 146 589       |
| <b>Type C</b> | 0              | 11            | 3              | 69 619        |

The substance/substance group *Magnesium stearate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.7778 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.7143 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested

reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20707     | 21084               | 13.60                        | 38.32                           |
| 21084     | 21084               | 0.00                         | 45.58                           |
| 21117     | 21084               | 25.54                        | 67.50                           |
| 21783     | 21783               | 0.00                         | 29.58                           |
| 22817     | 21783               | 4.36                         | 36.23                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Manganese orotate dihydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22311-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Manganese orotate dihydrate

### Special notes

When selecting the *Manganese orotate dihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Manganese orotate dihydrate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Euro OTC | Manganese orotat... | 1601003    | 22311     | 40      | 20160113*   |
| Euro OTC | Manganese orotat... | 1605029-01 | 22654     | 40      | 20160624    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Manganese orotate dihydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *Manganese orotate dihydrate*.

| Supplier | Substance                   | Batch      | Sample ID          | Spectra |
|----------|-----------------------------|------------|--------------------|---------|
| Euro OTC | Manganese orotate dihydrate | 1601003    | 22311 <sup>†</sup> | 20      |
| Euro OTC | Manganese orotate dihydrate | 1605029-01 | 22737              | 40      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Manganese orotate dihydrate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Manganese orotate dihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Manganese orotate dihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Manganese orotate dihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22311     | 22311               | 0.00                         | 53.18                           |
| 22654     | 22311               | 15.59                        | 53.86                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Mannitole**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20118-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Mannitole; Mannitolium

### Special notes

When selecting the *Mannitole* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Mannitole*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Caelo    | Mannitole | 12305723         | 20980     | 40      | 1402329     |
| Euro OTC | Mannitole | 1508012          | 21884     | 40      | 20150827*   |
| Euro OTC | Mannitole | 1511025          | 22286     | 40      | 20151228*   |
| Caelo    | Mannitole | 15197305         | 22581     | 40      | 20150720    |
| Fagron   | Mannitole | 15A26-B01-305841 | 22883     | 40      | 20150204    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Mannitole*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 730 spectra of 19 reference samples from the substance/substance group *Mannitole*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Caelo    | Mannitole | 9204712          | 20118              | 40      |
| Caelo    | Mannitole | 10100026         | 20130              | 40      |
| Euro OTC | Mannitole | 1508012          | 21884 <sup>†</sup> | 20      |
| Euro OTC | Mannitole | 1511025          | 22286 <sup>†</sup> | 20      |
| Caelo    | Mannitole | 160140           | 22458              | 60      |
| Euro OTC | Mannitole | 1604008          | 22515              | 40      |
| Caelo    | Mannitole | 16014013         | 22580              | 40      |
| Caelo    | Mannitole | 162009           | 22614              | 40      |
| Euro OTC | Mannitole | 1606031          | 22697              | 40      |
| Caelo    | Mannitole | 162121           | 22721              | 40      |
| Euro OTC | Mannitole | 1610027          | 22862              | 40      |
| Fagron   | Mannitole | 15A26-B01-305841 | 22884              | 40      |
| Caelo    | Mannitole | 162121           | 23066              | 30      |
| Euro OTC | Mannitole | 1703043          | 23125              | 40      |
| Caelo    | Mannitole | 170879           | 23296              | 40      |
| Caelo    | Mannitole | 160140           | 23299              | 40      |
| Caelo    | Mannitole | 170879           | 23305              | 40      |
| Caelo    | Mannitole | 170450           | 23318              | 40      |
| Euro OTC | Mannitole | 1708005          | 23700              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 145 999 spectra from a total of 3178 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 899 spectra from 221 *Apo-Ident* customers from 240 batches from the substance/substance group *Mannitole*.

| Supplier   | Substance | Batch            | Spectra |
|------------|-----------|------------------|---------|
| Caelo      | Mannitole | 13189227         | 11      |
| Caelo      | Mannitole | 14051209         | 9       |
| Caelo      | Mannitole | 14051231         | 1       |
| Fagron     | Mannitole | 14G04-B07-296196 | 1       |
| Caelo      | Mannitole | 14323138         | 15      |
| Euro OTC   | Mannitole | 1502022-01       | 13      |
| Caelo      | Mannitole | 15197313         | 8       |
| Caelo      | Mannitole | 12305709         | 20      |
| Caelo      | Mannitole | 12305710         | 11      |
| Caelo      | Mannitole | 12305723         | 5       |
| Caelo      | Mannitole | 1230578          | 1       |
| Phagron    | Mannitole | 1302C004-279405  | 1       |
| Euro OTC   | Mannitole | 1305043-01       | 15      |
| Caelo      | Mannitole | 16011402         | 1       |
| Klenk      | Mannitole | 5224A110314      | 1       |
| Caelo      | Mannitole | 9204719          | 2       |
| Caelo      | Mannitole | 10293140         | 1       |
| Caelo      | Mannitole | 10100026         | 3       |
| Caelo      | Mannitole | 11003611         | 1       |
| Euro OTC   | Mannitole | 1104028-01       | 1       |
| Euro OTC   | Mannitole | 1110009-01       | 13      |
| Euro OTC   | Mannitole | 1110009-02       | 6       |
| Noweda     | Mannitole | 11219101         | 2       |
| Caelo      | Mannitole | 11219114         | 3       |
| Noweda     | Mannitole | 11219115         | 2       |
| Caelo      | Mannitole | 11219122         | 1       |
| Caelo      | Mannitole | 11219121         | 1       |
| Noweda     | Mannitole | 11219124         | 1       |
| Caelo      | Mannitole | 11219124         | 4       |
| Noweda     | Mannitole | 11219138         | 1       |
| Caelo      | Mannitole | 11308807         | 2       |
| Euro OTC   | Mannitole | 1205016-01       | 19      |
| Phönix     | Mannitole | 120501602        | 1       |
| Phönix     | Mannitole | 12051601         | 1       |
| Sino Phyto | Mannitole | 12105403         | 1       |
| Caelo      | Mannitole | 12105403         | 3       |
| Noweda     | Mannitole | 12105404         | 1       |
| Caelo      | Mannitole | 12105404         | 5       |
| Noweda     | Mannitole | 12105405         | 1       |
| Caelo      | Mannitole | 12105420         | 6       |
| Großhandel | Mannitole | 12105420         | 1       |
| Noweda     | Mannitole | 12105421         | 3       |
| Caelo      | Mannitole | 12105421         | 11      |
| Caelo      | Mannitole | 12105433         | 11      |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------|------------------|----------------|
| cesar&lorentz/Phönix       | Mannitole        | 12305710         | 1              |
| Phönix                     | Mannitole        | 12305723         | 1              |
| Caelo                      | Mannitole        | 12305724         | 4              |
| Caelo                      | Mannitole        | 12305725         | 18             |
| Caelo                      | Mannitole        | 12305726         | 1              |
| Caelo                      | Mannitole        | 12305736         | 4              |
| Caelo                      | Mannitole        | 12305734         | 2              |
| Caelo                      | Mannitole        | 12305740         | 2              |
| Caelo                      | Mannitole        | 1305043-02       | 3              |
| Euro OTC                   | Mannitole        | 1310004-02       | 7              |
| Caelo                      | Mannitole        | 13189201         | 9              |
| Euro OTC                   | Mannitole        | 1305043-02       | 14             |
| Caelo                      | Mannitole        | 13189203         | 10             |
| Caelo                      | Mannitole        | 13189206         | 1              |
| Caelo                      | Mannitole        | 13189215         | 18             |
| Caelo                      | Mannitole        | 13189226         | 4              |
| Fagron                     | Mannitole        | 13K20-B01-287700 | 3              |
| Alliance Health 12.08.2... | Mannitole        | 1404034-01       | 2              |
| Caelo                      | Mannitole        | 14051204         | 8              |
| Caelo                      | Mannitole        | 14051205         | 7              |
| Caelo                      | Mannitole        | 14051215         | 8              |
| Phönix                     | Mannitole        | 14051215         | 1              |
| Euro OTC                   | Mannitole        | 1409016-01       | 19             |
| Euro OTC                   | Mannitole        | 1409016-02       | 3              |
| Caelo                      | Mannitole        | 1423120          | 1              |
| Caelo                      | Mannitole        | 14323103         | 3              |
| Caelo                      | Mannitole        | 14323115         | 3              |
| Caelo                      | Mannitole        | 14323105         | 3              |
| Caelo                      | Mannitole        | 14323120         | 1              |
| Caelo                      | Mannitole        | 14323129         | 1              |
| Fagron                     | Mannitole        | 14G04-B07        | 2              |
| Euro OTC                   | Mannitole        | 1502022-02       | 6              |
| Caelo                      | Mannitole        | 15184101         | 1              |
| Euro OTC                   | Mannitole        | 1511025-01       | 26             |
| Caelo                      | Mannitole        | 15197302         | 5              |
| Caelo                      | Mannitole        | 15197314         | 2              |
| Fagron                     | Mannitole        | 15A26-B01-304717 | 2              |
| Fagron                     | Mannitole        | 16824-B08-318962 | 1              |
| Euro OTC                   | Mannitole        | 1606031-01       | 9              |
| Caelo                      | Mannitole        | 15K25-B04        | 1              |
| Caelo                      | Mannitole        | 20151012-2       | 1              |
| xxxxx                      | Mannitole        | xxxx             | 1              |
| Euro OTC                   | Mannitole        | 17/14            | 1              |
| Caelo                      | Mannitole        | 2101401          | 1              |
| Caelo                      | Mannitole        | 2274635          | 1              |
| Caelo                      | Mannitole        | 5031304          | 1              |
| Caelo                      | Mannitole        | 7071404          | 1              |
| Caelo                      | Mannitole        | 9081303          | 1              |
| Caelo                      | Mannitole        | 10011501         | 1              |
| Euro OTC                   | Mannitole        | 1006019-01       | 1              |
| Euro OTC                   | Mannitole        | 10112014E        | 1              |
| Euro OTC                   | Mannitole        | 1006019-02       | 1              |
| Gehe                       | Mannitole        | 110009-02        | 1              |
| stumpf                     | Mannitole        | 1104028-02       | 1              |
| Euro OTC                   | Mannitole        | 1104028-03       | 4              |
| EuRho                      | Mannitole        | 1104028-03       | 1              |
| ANZAG am 11.05.2012        | Mannitole        | 1104028-03       | 2              |
| Klenk                      | Mannitole        | 110402803        | 1              |
| Caelo                      | Mannitole        | 1110009-02       | 1              |
| Caelo                      | Mannitole        | 11219101         | 2              |

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| <b>Supplier</b>      | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|----------------------|------------------|--------------|----------------|
| Euro OTC             | Mannitole        | 111100009-02 | 1              |
| Fagron               | Mannitole        | 11219122     | 1              |
| Fagron               | Mannitole        | 11L19-N15    | 1              |
| Caelo                | Mannitole        | 1205016-01   | 2              |
| Euro OTC             | Mannitole        | 1205016      | 1              |
| Caelo                | Mannitole        | 11D01-N10    | 1              |
| Gehe                 | Mannitole        | 1205016-01   | 1              |
| phönix, 13.11.2012   | Mannitole        | 1205016-01   | 2              |
| EuRho                | Mannitole        | 1205016-01   | 1              |
| Noweda               | Mannitole        | 1205016-02   | 2              |
| Euro OTC             | Mannitole        | 1205016-02   | 3              |
| Gehe/ Eurho          | Mannitole        | 1205016-02   | 1              |
| Caelo                | Mannitole        | 1205016-02   | 2              |
| Anzag 25.02.13       | Mannitole        | 1205016-02   | 1              |
| Phoenix              | Mannitole        | 120501602    | 1              |
| Linden-Apotheke      | Mannitole        | 1205016-02   | 1              |
| Caelo                | Mannitole        | 12105405     | 2              |
| Caelo                | Mannitole        | 12105438     | 1              |
| Großhandel           | Mannitole        | 12105438     | 3              |
| gehe 14.08.2013      | Mannitole        | 1211034      | 1              |
| Euro OTC             | Mannitole        | 1211034-01   | 10             |
| Euro OTC             | Mannitole        | 121103401    | 1              |
| Caelo                | Mannitole        | 1211034-01   | 1              |
| ANZAG                | Mannitole        | 1211034-01   | 1              |
| Caelo                | Mannitole        | 121103401    | 1              |
| EuRho                | Mannitole        | 1211034-01   | 1              |
| Klenk                | Mannitole        | 1211034-02   | 2              |
| Euro OTC             | Mannitole        | 1211034-02   | 19             |
| Phönix               | Mannitole        | 1211034-02   | 1              |
| Caelo                | Mannitole        | 1211034-02   | 1              |
| Großhandel           | Mannitole        | 12305710     | 1              |
| Hirsch               | Mannitole        | 12305725     | 1              |
| Caelo                | Mannitole        | 12305728     | 1              |
| Fagron               | Mannitole        | 12E24-N03    | 1              |
| Gehe                 | Mannitole        | 12E24-N08    | 1              |
| Fagron               | Mannitole        | 12E24-N08    | 1              |
| Gehe                 | Mannitole        | 12J26-N15    | 1              |
| Fagron               | Mannitole        | 12J26-N15    | 2              |
| Fagron               | Mannitole        | 12K28-N01    | 1              |
| Fagron               | Mannitole        | 1302C004     | 2              |
| Fagron               | Mannitole        | 1302C005     | 1              |
| Euro OTC             | Mannitole        | 1305043      | 1              |
| gehe 10.12.13        | Mannitole        | 1305043/01   | 1              |
| Euro OTC             | Mannitole        | 130504301    | 1              |
| Phönix               | Mannitole        | 1305043-01   | 1              |
| Noweda               | Mannitole        | 1305043-01   | 1              |
| GEHE                 | Mannitole        | 130504301    | 1              |
| Euro OTC             | Mannitole        | 131000401    | 1              |
| Euro OTC             | Mannitole        | 1310004-01   | 12             |
| Phoenix              | Mannitole        | 1310004-01   | 1              |
| Caelo                | Mannitole        | 1310004-01   | 4              |
| PHOENIX 24.04.2014   | Mannitole        | 1310004-01   | 3              |
| Sanacorp             | Mannitole        | 1310004-01   | 1              |
| Apomix               | Mannitole        | 1310004-01   | 1              |
| GEHE 24.07.2014      | Mannitole        | 1310004-02   | 1              |
| Euro OTC             | Mannitole        | 13155710     | 1              |
| Caelo                | Mannitole        | 13189207     | 7              |
| Caesar & Loretz GmbH | Mannitole        | 13189207     | 1              |
| Caelo                | Mannitole        | 13189208     | 5              |
| Fagron               | Mannitole        | 13189208     | 1              |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|----------------------------|------------------|-------------------|----------------|
| Sanacorp                   | Mannitole        | 13189215          | 1              |
| Fagron                     | Mannitole        | 13B01-B05-283812  | 1              |
| Caelo                      | Mannitole        | 13189228          | 1              |
| Gehe                       | Mannitole        | 13E24-N01         | 1              |
| Fagron                     | Mannitole        | 13B01-B05-287705  | 1              |
| Fagron                     | Mannitole        | 13E24N01          | 1              |
| Fagron                     | Mannitole        | 13K20-B01         | 1              |
| Fagron                     | Mannitole        | 13K20-B01-287698  | 2              |
| Fagron                     | Mannitole        | 13K20-B01-294193  | 1              |
| Caelo                      | Mannitole        | 13K20-B01-287704  | 1              |
| Fagron                     | Mannitole        | 13K20-B01-294194  | 2              |
| Euro OTC                   | Mannitole        | 14003402          | 1              |
| Caelo                      | Mannitole        | 1400434-01        | 1              |
| Euro OTC                   | Mannitole        | 1404034-01        | 21             |
| Caelo                      | Mannitole        | 1404034-01        | 2              |
| EuRho                      | Mannitole        | 1404034-01        | 1              |
| Euro OTC                   | Mannitole        | 140403401         | 2              |
| EuRhoPha                   | Mannitole        | 1404034-01        | 1              |
| Gehe                       | Mannitole        | 1404034-01        | 1              |
| Euro OTC                   | Mannitole        | 1404034-02        | 16             |
| EuRho                      | Mannitole        | 1404034-02        | 2              |
| Caelo                      | Mannitole        | 14051216          | 2              |
| Caelo                      | Mannitole        | 14051229          | 5              |
| Caelo                      | Mannitole        | 14051223          | 1              |
| Lamotte/Phoenix            | Mannitole        | 1409016-01        | 1              |
| Euro OTC                   | Mannitole        | 1409016-1         | 1              |
| Noweda29.04.2015           | Mannitole        | 14323113          | 1              |
| Caelo                      | Mannitole        | 14323113          | 1              |
| Caelo                      | Mannitole        | 14323114          | 3              |
| Caesar & Loretz GmbH       | Mannitole        | 14323119          | 1              |
| Caelo                      | Mannitole        | 14323121          | 6              |
| Caelo                      | Mannitole        | 14323124          | 2              |
| Noweda                     | Mannitole        | 14323124          | 1              |
| Caelo                      | Mannitole        | 14323125          | 1              |
| Caelo                      | Mannitole        | 14323126          | 3              |
| Caelo                      | Mannitole        | 14323127          | 2              |
| cealo/phoenix              | Mannitole        | 14323138          | 2              |
| Cael Sanacorp 05.02.2016   | Mannitole        | 14323138          | 2              |
| Fagron                     | Mannitole        | 14G004-B07-301692 | 1              |
| Fagron                     | Mannitole        | 14G04-B07-301693  | 1              |
| Fagron                     | Mannitole        | 14G04-B07-301694  | 1              |
| Fagron                     | Mannitole        | 14G17-B06-301921  | 1              |
| Fagron                     | Mannitole        | 15/24-B04-314324  | 1              |
| Euro OTC                   | Mannitole        | 15002022-01       | 1              |
| Euro OTC                   | Mannitole        | 1502022/01        | 1              |
| Fagron                     | Mannitole        | 1502022-01        | 3              |
| Allianz Healthcare 26.0... | Mannitole        | 1502022-01        | 1              |
| Caelo                      | Mannitole        | 1502022-01        | 1              |
| Euro OTC                   | Mannitole        | 150202201         | 2              |
| EuRho                      | Mannitole        | 1502022-02        | 1              |
| Euro/Phönix                | Mannitole        | 1502022-02        | 1              |
| Euro OTC                   | Mannitole        | 150202202         | 1              |
| Euro OTC                   | Mannitole        | 1508012-01        | 15             |
| EuRho                      | Mannitole        | 1508012-01        | 5              |
| Caelo                      | Mannitole        | 1508012-01        | 3              |
| Roquette Lestrem/Noweda    | Mannitole        | 1508012-01        | 1              |
| Euro OTC                   | Mannitole        | 1508012-02        | 8              |
| EuRho                      | Mannitole        | 1508012-02        | 1              |
| Euro OTC                   | Mannitole        | 151025-01         | 1              |
| Euro OTC                   | Mannitole        | 151102501         | 2              |

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| <b>Supplier</b>         | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|-------------------------|------------------|------------------|----------------|
| Roquette Lestrem/Noweda | Mannitole        | 1511025-01       | 1              |
| Caelo                   | Mannitole        | 15197301         | 7              |
| Caelo                   | Mannitole        | 1519713          | 1              |
| Euro OTC                | Mannitole        | 151105-01        | 1              |
| Caelo                   | Mannitole        | 15197303         | 1              |
| Celo                    | Mannitole        | 15197313         | 1              |
| Phoenix                 | Mannitole        | 15197314         | 1              |
| Euro OTC                | Mannitole        | 158012-01        | 1              |
| Caelo                   | Mannitole        | 15197319         | 1              |
| Caelo                   | Mannitole        | 15525            | 1              |
| Fargon/ Noweda          | Mannitole        | 15A26-B01-304717 | 1              |
| Fargon                  | Mannitole        | 15B05-B04-304084 | 3              |
| Fargon                  | Mannitole        | 15B05-B06-304302 | 1              |
| Noweda                  | Mannitole        | 15B05-B06-304302 | 1              |
| Caelo                   | Mannitole        | 15D28-B02-309192 | 1              |
| Caelo                   | Mannitole        | 15B05-B09-304305 | 1              |
| Noweda                  | Mannitole        | 15I24-B05-314323 | 1              |
| sanacorp                | Mannitole        | 15K17-B01-315560 | 1              |
| Noweda                  | Mannitole        | 15K17-B01        | 1              |
| Fargon                  | Mannitole        | 15K17-B03-314903 | 1              |
| Fargon                  | Mannitole        | 15K25-B04-317786 | 1              |
| Fargon                  | Mannitole        | 15K25-B06-318740 | 1              |
| Noweda                  | Mannitole        | 15I24-B05-314323 | 1              |
| Caelo                   | Mannitole        | 16200924         | 1              |
| Fargon                  | Mannitole        | 16/28-B01-328593 | 1              |
| Euro OTC                | Mannitole        | 160027-01        | 1              |
| Euro OTC                | Mannitole        | 16006031-01      | 1              |
| Caelo                   | Mannitole        | 16014005         | 1              |
| Caelo                   | Mannitole        | 16014014         | 1              |
| Caelo                   | Mannitole        | 16014016         | 1              |
| Euro OTC                | Mannitole        | 1604002-01       | 1              |
| Euro OTC                | Mannitole        | 1604008          | 1              |
| Defektur/eigen          | Mannitole        | 1604008-01       | 1              |
| Euro OTC                | Mannitole        | 1604008-01       | 15             |
| Caelo                   | Mannitole        | 1604008-01       | 1              |
| Euro OTC                | Mannitole        | 160601-01        | 1              |
| Euro OTC                | Mannitole        | 1606031-02       | 3              |
| Caelo                   | Mannitole        | 1606031-02       | 1              |
| Caelo                   | Mannitole        | 16061401         | 1              |
| Euro OTC                | Mannitole        | 1610027-01       | 8              |
| Caelo                   | Mannitole        | 16200904         | 2              |
| Caelo                   | Mannitole        | 16200908         | 2              |
| Caelo                   | Mannitole        | 16200909         | 1              |
| Caelo                   | Mannitole        | 16200912         | 1              |
| Caelo                   | Mannitole        | 16200913         | 1              |
| Caelo                   | Mannitole        | 16200914         | 2              |
| Caelo                   | Mannitole        | 16212101         | 5              |
| Caelo                   | Mannitole        | 16212102         | 4              |
| PHÖNIX                  | Mannitole        | 16212102         | 1              |
| Fargon                  | Mannitole        | 16212103         | 1              |
| Caelo                   | Mannitole        | 16212103         | 1              |
| Caelo                   | Mannitole        | 16212104         | 1              |
| Caelo                   | Mannitole        | 16212109         | 1              |
| Caelo                   | Mannitole        | 16340301         | 5              |
| Caelo                   | Mannitole        | 16B24-09-320013  | 1              |
| Fargon/Sanacorp         | Mannitole        | 16B24-B09-320013 | 1              |
| Fargon                  | Mannitole        | 16E11-B07-322830 | 2              |
| Fargon                  | Mannitole        | 16F27-Bo5-324517 | 1              |
| Fargon                  | Mannitole        | 16H29-B05-327813 | 1              |
| Fargon                  | Mannitole        | 170980-0002      | 1              |

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| Supplier             | Substance | Batch               | Spectra |
|----------------------|-----------|---------------------|---------|
| Fragron/Noweda       | Mannitole | 17A12-B04-330729    | 1       |
| Fagron               | Mannitole | 16H25-B03-326639    | 1       |
| EuRho                | Mannitole | 1911M-01844         | 1       |
| Caelo                | Mannitole | 23082013C           | 1       |
| Caelo                | Mannitole | 2713M-01844         | 2       |
| Caelo                | Mannitole | 24101306            | 1       |
| Caelo                | Mannitole | 30031502            | 1       |
| Caelo                | Mannitole | 30121417            | 1       |
| Caelo                | Mannitole | 4414E-01844         | 1       |
| Caelo                | Mannitole | 48558               | 1       |
| Euro OTC             | Mannitole | E671Z               | 1       |
| Fagron               | Mannitole | 720014-0002         | 1       |
| Fagron               | Mannitole | E616X               | 1       |
| Fagron               | Mannitole | E717A               | 1       |
| Euro OTC             | Mannitole | T03-07/1409016-01   | 1       |
| Anzag                | Mannitole | 111000902           | 1       |
| Caelo                | Mannitole | 12305725-344431112  | 1       |
| Fagron               | Mannitole | 1302C004-279405     | 1       |
| Fagron               | Mannitole | 1302c005            | 1       |
| EuRho/Sanac          | Mannitole | 1305043-01          | 1       |
| Caelo                | Mannitole | 13095013            | 1       |
| Gutenberg-Apotheke   | Mannitole | 1310004-01          | 4       |
| Gutenberg-Apotheke   | Mannitole | 1310004-02          | 1       |
| Caelo                | Mannitole | 13189203-3566412081 | 1       |
| Euro OTC             | Mannitole | 13189216            | 2       |
| Gutenberg-Apotheke   | Mannitole | 13189221            | 1       |
| Caelo                | Mannitole | 13189222            | 3       |
| VDL;21.11.14;3,98EUR | Mannitole | 13189227            | 1       |
| Fagron               | Mannitole | 13B01-B05-283811    | 2       |
| Fagron               | Mannitole | 13K20-B01-292064    | 2       |
| Caelo                | Mannitole | 14051207            | 1       |
| Caelo                | Mannitole | 14051208            | 2       |
| Caelo                | Mannitole | 14051217            | 2       |
| Caelo                | Mannitole | 14051224            | 2       |
| Caelo                | Mannitole | 14051230            | 2       |
| Euro OTC             | Mannitole | 14323101            | 3       |
| Caelo                | Mannitole | 1405127             | 1       |
| Fagron               | Mannitole | 15K17-B01-315560    | 1       |
| Caelo                | Mannitole | 1612101             | 1       |
| Fagron               | Mannitole | E687X               | 1       |
| Caelo                | Mannitole | P154/14             | 1       |

- 68 734 spectra from 413 *Apo-Ident* customers from a total of 23 571 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Mannitole* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Mannitole* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).



|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 200           | 0              | 71 186        |
| Type B | 0              | 730           | 0              | 145 879       |
| Type C | 0              | 866           | 33             | 68 720        |

The substance/substance group *Mannitole* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 99.1781 %) |
| Type C | 100.0000 % (> 99.8814 %) | 96.3293 % (> 95.9956 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20980     | 20980               | 0.00                         | 51.33                           |
| 21884     | 21884               | 0.00                         | 50.61                           |
| 22286     | 22286               | 0.00                         | 50.08                           |
| 22581     | 22286               | 6.66                         | 51.65                           |
| 22883     | 21884               | 2.74                         | 51.52                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Melatonin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20553-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Melatonin; Melatoninum

### Special notes

When selecting the *Melatonin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Melatonin*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Caelo    | Melatonin | 12321404         | 20834     | 37      | 20121107    |
| Caelo    | Melatonin | 12321411         | 20835     | 40      | 20121107    |
| Caelo    | Melatonin | 12321415         | 20987     | 80      | 20121107    |
| Euro OTC | Melatonin | 1305029-02       | 21618     | 40      | 1411054     |
| Euro OTC | Melatonin | 1510041          | 22237     | 40      | 20151123*   |
| Fagron   | Melatonin | 15G06-B03-315183 | 22892     | 40      | 20150717    |
| Fagron   | Melatonin | 15G06-B03-323733 | 22893     | 40      | 20150717    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 317 spectra of 7 reference samples from the substance/substance group *Melatonin*. These samples are listed above in the [calibration samples](#) section.
- 71 069 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 380 spectra of 10 reference samples from the substance/substance group *Melatonin*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Caelo    | Melatonin | 9366205          | 20106              | 40      |
| Caelo    | Melatonin | 11267102         | 20553              | 40      |
| Euro OTC | Melatonin | 1305029-02       | 21618 <sup>†</sup> | 20      |
| Euro OTC | Melatonin | 1510041          | 22237 <sup>†</sup> | 20      |
| Euro OTC | Melatonin | 1610040          | 22871              | 40      |
| Caelo    | Melatonin | 163437           | 23036              | 40      |
| Euro OTC | Melatonin | 1510041          | 22237SI            | 60      |
| Fagron   | Melatonin | 15G06-B03-315183 | 22892SI            | 40      |
| Fagron   | Melatonin | 15G06-B03-323733 | 22893SI            | 40      |
| Caelo    | Melatonin | 163437           | 23036SI            | 40      |

- 146 349 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 291 spectra from 88 *Apo-Ident* customers from 114 batches from the substance/substance group *Melatonin*.

| Supplier            | Substance | Batch      | Spectra |
|---------------------|-----------|------------|---------|
| Caelo               | Melatonin | 10071303   | 1       |
| Caelo               | Melatonin | 10296623   | 1       |
| Cealo/Gehe          | Melatonin | 10296624   | 1       |
| Gehe                | Melatonin | 11/26-N07  | 1       |
| Inresa              | Melatonin | 110005     | 1       |
| ANZAG am 30.04.2012 | Melatonin | 11267102   | 1       |
| Noweda              | Melatonin | 11267102   | 2       |
| Caelo               | Melatonin | 11267108   | 1       |
| Phönix, 31.10.2012  | Melatonin | 11267109   | 1       |
| Caelo               | Melatonin | 11267109   | 4       |
| Phönix Gotha        | Melatonin | 11267110   | 2       |
| Caelo               | Melatonin | 11267110   | 1       |
| Noweda              | Melatonin | 11267111   | 1       |
| Caelo               | Melatonin | 11267114   | 1       |
| Anzag 20.12.12      | Melatonin | 11267114   | 2       |
| Caelo               | Melatonin | 11267111   | 1       |
| Caelo               | Melatonin | 11267119   | 1       |
| Noweda              | Melatonin | 11267119   | 1       |
| Sanacorp            | Melatonin | 11267119   | 1       |
| Phönix Gotha        | Melatonin | 11267120   | 1       |
| Caelo               | Melatonin | 11267120   | 4       |
| Caelo               | Melatonin | 11267121   | 4       |
| Gehe 10.04.2013     | Melatonin | 11267121   | 1       |
| Caelo               | Melatonin | 11267122   | 2       |
| Noweda              | Melatonin | 11267126   | 1       |
| Caelo               | Melatonin | 11267126   | 3       |
| Fagron              | Melatonin | 11F09-N02  | 1       |
| Gehe                | Melatonin | 11L21-N04  | 1       |
| Caelo               | Melatonin | 120009     | 1       |
| Euro OTC            | Melatonin | 120008     | 1       |
| Euro OTC            | Melatonin | 12001      | 2       |
| Anzag 10.08.2012    | Melatonin | 1204003-01 | 1       |
| Euro OTC            | Melatonin | 1204003-02 | 14      |
|                     | Melatonin | 1204003-02 | 2       |
| Euro OTC            | Melatonin | 120400302  | 1       |
| Phönix 02.01.2014   | Melatonin | 1204003-02 | 1       |
| 10 17.07.2013       | Melatonin | 1231415    | 1       |
| Caelo               | Melatonin | 12321404   | 3       |
| Caelo               | Melatonin | 12321406   | 6       |
| Gehe am 20.03.2013  | Melatonin | 12321406   | 1       |
| Caelo               | Melatonin | 12321415   | 3       |
| Caelo               | Melatonin | 12321411   | 2       |
| gehe 12.09.13       | Melatonin | 12321415   | 1       |
| Caelo               | Melatonin | 12321416   | 6       |
| Caelo               | Melatonin | 12321422   | 6       |
| Caelo               | Melatonin | 12321421   | 2       |
| Anzag 22.02.13      | Melatonin | 1267121    | 2       |
| Cealo               | Melatonin | 12321422   | 1       |
| Caelo               | Melatonin | 1296630    | 1       |
| Gehe                | Melatonin | 12G19-N03  | 2       |
| Fgron               | Melatonin | 12G19-N03  | 1       |
| Phoenix 03.04.2014  | Melatonin | 12J19-N02  | 1       |

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| <b>Supplier</b>    | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|--------------------|------------------|------------------|----------------|
| Fagron             | Melatonin        | 12K13-N02        | 1              |
| Fagron             | Melatonin        | 1305029-01       | 1              |
| Euro OTC           | Melatonin        | 1305029-01       | 12             |
| Euro OTC           | Melatonin        | 1305092-01       | 1              |
| Caelo              | Melatonin        | 13167301         | 10             |
| Phönix 19.02.2014  | Melatonin        | 13167301         | 2              |
| gehe               | Melatonin        | 13167301         | 1              |
| GEHE 22.03.2014    | Melatonin        | 13167302         | 1              |
| Caelo              | Melatonin        | 13167302         | 1              |
| Caelo              | Melatonin        | 13167309         | 1              |
| Caelo              | Melatonin        | 13167310         | 1              |
| Caelo              | Melatonin        | 13167312         | 3              |
| Caelo              | Melatonin        | 13167314         | 7              |
| Fagron             | Melatonin        | 13D12N10         | 1              |
| Fagron             | Melatonin        | 13D12-N10        | 2              |
| Gehe               | Melatonin        | 13D12-N10        | 1              |
| Fagron             | Melatonin        | 13e22-n12        | 1              |
| Gehe               | Melatonin        | 13E22-N12        | 1              |
| Fagron             | Melatonin        | 13E22N12         | 1              |
| PHOENIX 14.04.2014 | Melatonin        | 13E22-N12        | 1              |
| Fagron             | Melatonin        | 13E22-N12        | 1              |
| Fagron             | Melatonin        | 13H21-N06        | 4              |
| Fagron             | Melatonin        | 13H21-N065x      | 1              |
| Phönix 02.01.15    | Melatonin        | 13H21-N06        | 1              |
| Fagron             | Melatonin        | 13H29-B03-291180 | 5              |
| Fagron             | Melatonin        | 13H29-B03        | 1              |
| Koisser            | Melatonin        | 140202           | 2              |
| Cactus Botanics    | Melatonin        | 140610-C061      | 1              |
| Euro OTC           | Melatonin        | 1407028-02       | 2              |
| Euro OTC           | Melatonin        | 1407028-01       | 1              |
| Caelo              | Melatonin        | 14110302         | 2              |
| Caelo              | Melatonin        | 14110303         | 1              |
| Caelo              | Melatonin        | 14110305         | 2              |
| Caelo              | Melatonin        | 14110308         | 3              |
| Caelo              | Melatonin        | 14110314         | 1              |
| Caelo              | Melatonin        | 14110316         | 2              |
| Fagron             | Melatonin        | 14G18-B01-297242 | 1              |
| Fagron             | Melatonin        | 14G18-B01-297245 | 3              |
| Caelo              | Melatonin        | 150601           | 1              |
| Fagron             | Melatonin        | 14G18-B01-297244 | 1              |
| Caelo              | Melatonin        | 15093001         | 6              |
| Caelo              | Melatonin        | 15093002         | 2              |
| Caelo              | Melatonin        | 15093004         | 1              |
| Caelo              | Melatonin        | 15093008         | 3              |
| Caelo              | Melatonin        | 15093010         | 3              |
| Euro OTC           | Melatonin        | 1510041-01       | 3              |
| Caelo              | Melatonin        | 1524309          | 1              |
| Caelo              | Melatonin        | 1514E-03554      | 1              |
| Caelo              | Melatonin        | 15254305         | 4              |
| Caelo              | Melatonin        | 15254306         | 7              |
| Caelo              | Melatonin        | 15254307         | 3              |
| Caelo              | Melatonin        | 15254308         | 7              |
| Caelo              | Melatonin        | 15254313         | 1              |
| Euro OTC           | Melatonin        | 15254316         | 1              |
| Caelo              | Melatonin        | 15254319         | 2              |
| Caelo              | Melatonin        | 15254320         | 3              |
| Caelo              | Melatonin        | 15254324         | 3              |
| Caelo              | Melatonin        | 15254321         | 3              |
| Caelo              | Melatonin        | 15254328         | 2              |
| Alte Apotheke      | Melatonin        | 15254328         | 1              |

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| Supplier                | Substance | Batch            | Spectra |
|-------------------------|-----------|------------------|---------|
| Caelo                   | Melatonin | 15254331         | 2       |
| Caelo                   | Melatonin | 15254336         | 2       |
| Caelo                   | Melatonin | 15254338         | 4       |
| Phoenix                 | Melatonin | 15C20-B01        | 1       |
| Fagron                  | Melatonin | 15C20-B01-306077 | 1       |
| Fagron                  | Melatonin | 15C20-B01-306078 | 3       |
| Fagron                  | Melatonin | 15C20-B01-308426 | 1       |
| Fagron                  | Melatonin | 15C20-B01-308427 | 2       |
| Fagron                  | Melatonin | 15G06-B03-315183 | 1       |
| gepepharm               | Melatonin | 15G06-B03-315183 | 1       |
| Fagron                  | Melatonin | 15G06-B03-321298 | 1       |
| Caelo                   | Melatonin | 16121303         | 1       |
| Caelo                   | Melatonin | 16266901         | 2       |
| Caelo                   | Melatonin | 16266906         | 2       |
| Caelo                   | Melatonin | 16266909         | 2       |
| Caelo                   | Melatonin | 16266908         | 1       |
| Sanacorp                | Melatonin | 16266909         | 1       |
| Caelo                   | Melatonin | 16343709         | 1       |
| Fagron                  | Melatonin | 16G06-B01        | 1       |
| Caelo                   | Melatonin | 20021312         | 1       |
| Caelo                   | Melatonin | 20021505         | 1       |
| Caelo                   | Melatonin | 2313M03554       | 1       |
| Euro OTC                | Melatonin | CH1305029-01     | 1       |
| Farmalabor / Farmalabor | Melatonin | P1201556-000     | 1       |
| Caelo                   | Melatonin | 14110313         | 1       |
| KS Pharma               | Melatonin | XPS130428        | 1       |
| Caelo                   | Melatonin | 1126109          | 1       |
| Phönix                  | Melatonin | 11267111         | 1       |
| Caelo                   | Melatonin | 11267128         | 1       |
| Fagron                  | Melatonin | 120009           | 1       |
| Caelo                   | Melatonin | 12321403         | 1       |
| Fagron                  | Melatonin | 12G19-N03        | 1       |

- 69 342 spectra from 414 *Apo-Ident* customers from a total of 23 687 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Melatonin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Melatonin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 317           | 0              | 71 069        |
| <b>Type B</b> | 0              | 378           | 2              | 146 349       |
| <b>Type C</b> | 0              | 263           | 28             | 69 342        |

The substance/substance group *Melatonin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.1073 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.4737 % (> 98.6842 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 90.3780 % (> 89.3471 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20834     | 22237               | 23.85                        | 46.54                           |
| 20835     | 22237               | 4.45                         | 37.86                           |
| 20987     | 21618               | 2.76                         | 37.30                           |
| 21618     | 21618               | 0.00                         | 37.64                           |
| 22237     | 22237               | 0.00                         | 37.72                           |
| 22892     | 22237               | 3.10                         | 37.17                           |
| 22893     | 22237               | 4.65                         | 36.76                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Menthol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20036-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Menthol; Levomentholum; Mentholum

### Special notes

When selecting the *Menthol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Menthol*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Caelo    | Menthol   | 13377404         | 21443     | 40      | 20131212    |
| Euro OTC | Menthol   | 1403022-02       | 21601     | 30      | 20140408    |
| Euro OTC | Menthol   | 1509045          | 21932     | 40      | 20151008*   |
| Euro OTC | Menthol   | 1603024          | 22657     | 40      | 20160429*   |
| Euro OTC | Menthol   | 1608012          | 22825     | 40      | 20160902*   |
| Fagron   | Menthol   | 16L20-T04-044769 | 23596     | 40      | 20170116    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 230 spectra of 6 reference samples from the substance/substance group *Menthol*. These samples are listed above in the [calibration samples](#) section.
- 71 156 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 420 spectra of 12 reference samples from the substance/substance group *Menthol*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Caelo    | Menthol   | 82621209   | 20036              | 30      |
| Caelo    | Menthol   | 82621429   | 20078              | 20      |
| Caelo    | Menthol   | 10157605   | 20273              | 40      |
| Caelo    | Menthol   | 13377404   | 21443 <sup>†</sup> | 20      |
| Euro OTC | Menthol   | 1403022-02 | 21601 <sup>†</sup> | 30      |
| Euro OTC | Menthol   | 1509045    | 21932 <sup>†</sup> | 20      |
| Caelo    | Menthol   | 160956     | 22452              | 60      |
| Euro OTC | Menthol   | 1701014    | 23005              | 40      |
| Caelo    | Menthol   | 170927     | 23312              | 40      |
| Euro OTC | Menthol   | 1705022    | 23427              | 40      |
| Caelo    | Menthol   | 170927     | 23645              | 40      |
| Caelo    | Menthol   | 171889     | 23668              | 40      |

- 146 309 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 534 spectra from 245 *Apo-Ident* customers from 159 batches from the substance/substance group *Menthol*.

| Supplier      | Substance | Batch       | Spectra |
|---------------|-----------|-------------|---------|
| Caelo         | Menthol   | 13377409    | 9       |
| Andreas Imhof | Menthol   | 8052015     | 1       |
| Fagron        | Menthol   | 13J21-N04   | 1       |
| Caelo         | Menthol   | 1403022-02  | 1       |
| Euro OTC      | Menthol   | 1410004-02  | 8       |
| Caelo         | Menthol   | 14183006    | 1       |
| Caelo         | Menthol   | 14183004    | 10      |
| Fagron        | Menthol   | 14H29-M02   | 9       |
| Caelo         | Menthol   | 15076101    | 8       |
| Euro OTC      | Menthol   | 1502006-02  | 13      |
| Caelo         | Menthol   | 15076112    | 10      |
| Fagron        | Menthol   | 15076113    | 2       |
| Caelo         | Menthol   | 15076113    | 3       |
| Caelo         | Menthol   | 15286216    | 1       |
| Caelo         | Menthol   | 15363803    | 1       |
| Caelo         | Menthol   | 15363815    | 4       |
| Imhof         | Menthol   | 15-5401     | 1       |
| Fagron        | Menthol   | 858607      | 1       |
| Caelo         | Menthol   | 314Q01855   | 1       |
| Fagron        | Menthol   | 11G19-N07   | 1       |
| Fagron        | Menthol   | 12/19-N10   | 2       |
| Euro OTC      | Menthol   | 120403602   | 3       |
| Euro OTC      | Menthol   | 1204036-01  | 10      |
| Fagron        | Menthol   | 12C05-N03   | 2       |
| Fagron        | Menthol   | 12G20-N02   | 5       |
| Euro OTC      | Menthol   | 1210017-01  | 5       |
| Caelo         | Menthol   | 13103901    | 27      |
| Fagron        | Menthol   | 13D16-N09   | 8       |
| Caelo         | Menthol   | 750137      | 1       |
| Anzag         | Menthol   | 12/19-N10   | 1       |
| Noweda        | Menthol   | 12020403    | 2       |
| Fagron        | Menthol   | 750137      | 2       |
| Euro OTC      | Menthol   | 120403601   | 1       |
| Fagron        | Menthol   | 12F01-N14   | 1       |
| Caelo         | Menthol   | 1320260     | 2       |
| Caelo         | Menthol   | 515A-01855  | 1       |
| Caelo         | Menthol   | 515M-01855  | 1       |
| Euro OTC      | Menthol   | 6102014B    | 1       |
| Finze         | Menthol   | 9221710     | 1       |
| Caelo         | Menthol   | 7111201     | 1       |
| Caelo         | Menthol   | 9221710     | 1       |
| Caelo         | Menthol   | 930716      | 1       |
| Caelo         | Menthol   | 10008029-02 | 1       |
| Caelo         | Menthol   | 1/AD1       | 1       |
| Euro OTC      | Menthol   | 1002019-03  | 1       |
| Euro OTC      | Menthol   | 1008029-01  | 1       |
| Caelo         | Menthol   | 10157615    | 1       |
| Euro OTC      | Menthol   | 1105028-01  | 1       |
| Caelo         | Menthol   | 11091405    | 1       |
| Euro OTC      | Menthol   | 1111020-01  | 1       |
| Caelo         | Menthol   | 1111020-01  | 4       |
| Euro OTC      | Menthol   | 1111020-02  | 1       |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|----------------------------|------------------|--------------|----------------|
| Caelo                      | Menthol          | 11202901     | 2              |
| Caelo                      | Menthol          |              | 1              |
| Caesar & Loretz GmbH, 4... | Menthol          | 11202910     | 1              |
| Caelo                      | Menthol          | 11202910     | 6              |
| Caelo                      | Menthol          | 11202907     | 1              |
| Caelo                      | Menthol          | 11202912     | 2              |
| Gehe/ 27.10.12 EuRho       | Menthol          | 11219216     | 1              |
| Caelo                      | Menthol          | 12020402     | 6              |
| Caesar & Loretz GmbH, 4... | Menthol          | 12020402     | 1              |
| Caelo                      | Menthol          | 12020403     | 1              |
| Caelo                      | Menthol          | 12020408     | 1              |
| Großhandel                 | Menthol          | 12020403     | 1              |
| Caesar/Noweda              | Menthol          | 12020403     | 1              |
| Caelo                      | Menthol          | 12020410     | 1              |
| Caelo                      | Menthol          | 12020411     | 8              |
| Caelo                      | Menthol          | 1202041      | 1              |
| Gehe                       | Menthol          | 12020411     | 1              |
| Euro OTC                   | Menthol          | 12020411     | 1              |
| Caesar & Loretz GmbH, 4... | Menthol          | 12020411     | 1              |
| Caelo                      | Menthol          | 1204036-01   | 1              |
| Noweda                     | Menthol          | 1204036-01   | 1              |
| Sanacorp                   | Menthol          | 1204036-01   | 1              |
| Gehe                       | Menthol          | 1204036-01   | 1              |
| Euro OTC                   | Menthol          | 120-4036-02  | 2              |
| Euro OTC                   | Menthol          | 1204036-02   | 3              |
| EuRho                      | Menthol          | 1204036-02   | 1              |
| euRho                      | Menthol          | 1204036-02   | 1              |
| Euro OTC                   | Menthol          | 1204036-1    | 1              |
| Sanacorp                   | Menthol          | 1210017-01   | 1              |
| Euro OTC                   | Menthol          | 1210017-02   | 11             |
| Phönix                     | Menthol          | 12246204     | 1              |
| Fagron                     | Menthol          | 1219-N10     | 1              |
| Caelo                      | Menthol          | 12246205     | 11             |
| Caelo                      | Menthol          | 12246204     | 1              |
| Anzag 03.05.2013           | Menthol          | 12246205     | 1              |
| Caelo                      | Menthol          | 12246211     | 3              |
| Caesar/Noweda              | Menthol          | 12246211     | 1              |
| Phoenix 15.04.2014         | Menthol          | 12246211     | 1              |
| v.d.l                      | Menthol          |              | 1              |
| FARGON                     | Menthol          | 12c05-n03    | 1              |
| Fagron                     | Menthol          | 12D23-N06    | 4              |
| Fagron                     | Menthol          | 12Cos-N03    | 1              |
| Fagron                     | Menthol          | 12I19-N10    | 2              |
| Frey*Lau GmbH              | Menthol          | 1305010-01   | 1              |
| Euro OTC                   | Menthol          | 1305010-01   | 9              |
| Caelo                      | Menthol          | 130501001    | 1              |
| AHD                        | Menthol          | 1305010-01   | 1              |
| Sanacorp                   | Menthol          | 1305010-01   | 1              |
| Alliance Health 14.04..14  | Menthol          | 1305010-02   | 1              |
| Euro OTC                   | Menthol          | 1305010-02   | 5              |
| Euro OTC                   | Menthol          | 130501002    | 1              |
| Europarm                   | Menthol          | 130501-01    | 1              |
| Retest                     | Menthol          | 1305010-02   | 1              |
| Caelo                      | Menthol          | 13103802     | 1              |
| Caesar & Loretz GmbH, 4... | Menthol          | 13103901     | 1              |
| Phönix 30.10.13            | Menthol          | 13103901     | 1              |
| Euro OTC                   | Menthol          | 1310J-01855  | 1              |
| Caelo                      | Menthol          | 13159104     | 3              |
| Caelo                      | Menthol          | 13159105     | 18             |
| Phönix                     | Menthol          | 13159105     | 1              |

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| Supplier                   | Substance | Batch              | Spectra |
|----------------------------|-----------|--------------------|---------|
| Caelo                      | Menthol   | 13377402           | 3       |
| Caelo                      | Menthol   | 13377404           | 13      |
| Caelo                      | Menthol   | 13377407           | 3       |
| Caelo                      | Menthol   | 13377408           | 4       |
| Caelo                      | Menthol   | 13377412           | 3       |
| Caelo                      | Menthol   | 13377413           | 2       |
| Gehe                       | Menthol   | 13377412           | 1       |
| Gehe                       | Menthol   | 13D16-N09          | 1       |
| Caelo                      | Menthol   | 13D16-N09          | 1       |
| Fagron                     | Menthol   | 13D16-N090631/1300 | 1       |
| Fagron                     | Menthol   | 13G09-N09          | 1       |
| Fagron                     | Menthol   | 13G09-N090204/520  | 1       |
| Fagron                     | Menthol   | 13D16-N09          | 1       |
| Euro OTC                   | Menthol   | 140302201          | 2       |
| Euro OTC                   | Menthol   | 1403022-01         | 3       |
| Euro OT                    | Menthol   | 1403022-01         | 1       |
| Euro OTC                   | Menthol   | 1403022-02         | 8       |
| Phoenix                    | Menthol   | 1403022-02         | 1       |
| Euro OTC                   | Menthol   | 140322-01          | 1       |
| Euro OTC                   | Menthol   | 14030222-02        | 1       |
| Euro OTC                   | Menthol   | 1410004-01         | 16      |
| Caelo                      | Menthol   | 1410004-01         | 1       |
| Euro OTC                   | Menthol   | 141000401          | 1       |
| Phönix Gotha               | Menthol   | 1410004-01         | 1       |
| Caelo                      | Menthol   | 1410004-02         | 1       |
| Caelo                      | Menthol   | 14183011           | 1       |
| Caelo                      | Menthol   | 14183008           | 3       |
| Caelo                      | Menthol   | 14183012           | 2       |
| Caelo                      | Menthol   | 14183014           | 4       |
| Caelo                      | Menthol   | 14183017           | 3       |
| Caelo                      | Menthol   | 14183020           | 1       |
| Fagron                     | Menthol   | 14H29-M04          | 1       |
| Euro OTC                   | Menthol   | 1502006-01         | 10      |
| Euro OTC                   | Menthol   | 150200601          | 1       |
| Fagron                     | Menthol   | 15076101           | 1       |
| Caelo                      | Menthol   | 15076106           | 5       |
| Caesar&Loretz,Phönix       | Menthol   | 15076106           | 1       |
| Caelo                      | Menthol   | 15076115           | 1       |
| Caelo                      | Menthol   | 15076215           | 1       |
| Euro OTC                   | Menthol   | 1509045            | 2       |
| Euro OTC                   | Menthol   | 1509045-01         | 2       |
| Euro OTC                   | Menthol   | 1509045-02         | 3       |
| Euro OTC                   | Menthol   | 150904502          | 1       |
| Euro OTC                   | Menthol   | 1509045-03         | 5       |
| Fagron                     | Menthol   | 1509045-03         | 1       |
| Frey & Lau GmbH/Noweda     | Menthol   | 1509045-03         | 2       |
| Norex Flavours Pvt. Ltd... | Menthol   | 15286205           | 1       |
| Norex Flavours Pvt. Ltd... | Menthol   | 15286207           | 1       |
| Caelo                      | Menthol   | 15363804           | 5       |
| Caelo                      | Menthol   | 15363805           | 3       |
| Noweda                     | Menthol   | 15363809           | 1       |
| Caelo                      | Menthol   | 15363809           | 4       |
| Caelo                      | Menthol   | 15363810           | 5       |
| Caelo                      | Menthol   | 1536815            | 1       |
| Euro OTC                   | Menthol   | 1603021-01         | 1       |
| Euro OTC                   | Menthol   | 1603024-01         | 12      |
| Caelo                      | Menthol   | 1603024-01         | 1       |
| Euro OTC                   | Menthol   | 1608012-01         | 8       |
| Euro OTC                   | Menthol   | 160801201          | 1       |
| Caelo                      | Menthol   | 1608012-02         | 1       |

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| Supplier            | Substance | Batch           | Spectra |
|---------------------|-----------|-----------------|---------|
| Euro OTC            | Menthol   | 1608012-02      | 3       |
| Euro OTC            | Menthol   | 1608012-12      | 1       |
| Gehe                | Menthol   | 16095602        | 1       |
| Caelo               | Menthol   | 16095603        | 1       |
| Caelo               | Menthol   | 16095606        | 3       |
| Caelo               | Menthol   | 16095613        | 4       |
| Caelo               | Menthol   | 16095614        | 1       |
| Fagron              | Menthol   | 1616Q-01855     | 1       |
| Euro OTC            | Menthol   | 1701014-01      | 2       |
| Euro OTC            | Menthol   | 170101402       | 1       |
| Caelo               | Menthol   | 19051401        | 1       |
| Caelo               | Menthol   | 25041402        | 1       |
| Caelo               | Menthol   | 1704211855      | 1       |
| Caelo               | Menthol   | 20200712-2      | 1       |
| Euro OTC            | Menthol   | 1701014-02      | 1       |
| Caelo               | Menthol   | 25051301        | 1       |
| Euro OTC            | Menthol   | 290601901       | 1       |
| EuRho               | Menthol   | 2910A-01855     | 1       |
| Caelo               | Menthol   | 3912A-01855     | 1       |
| Caelo               | Menthol   | 29121103        | 1       |
| Fagron              | Menthol   | 4611I-01855(NP) | 1       |
| Caelo               | Menthol   | 4810A-01855     | 1       |
| Caelo               | Menthol   | 5315I-01855     | 1       |
| Sanacorp            | Menthol   | 6/AKD3          | 1       |
| Euro OTC            | Menthol   | 696773          | 1       |
| Caelo               | Menthol   | 72173258        | 1       |
| Euro OTC            | Menthol   | 721123          | 2       |
| Phoenix             | Menthol   | 750137          | 1       |
| Euro OTC            | Menthol   | 807862          | 1       |
| Fagron              | Menthol   | 778301          | 1       |
| Euro OTC            | Menthol   | 858607          | 1       |
| Sanacorp            | Menthol   |                 | 1       |
| Euro OTC            | Menthol   | Ch1204036-02    | 1       |
| Caelo               | Menthol   | IntCh311052     | 1       |
| Caelo               | Menthol   | 814A-01855      | 1       |
| Frey+Lau GmbH, Gehe | Menthol   | 1305010-02      | 1       |
| Caelo               | Menthol   | 12246203        | 1       |
| Sanacorp            | Menthol   | 13103901        | 1       |
| Caelo               | Menthol   | 13159110        | 1       |
| Caelo               | Menthol   | 687711          | 1       |

- 69 099 spectra from 414 *Apo-Ident* customers from a total of 23 646 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Menthol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Menthol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 226           | 4              | 71 156        |
| Type B | 0              | 344           | 76             | 146 309       |
| Type C | 0              | 491           | 43             | 69 099        |

The substance/substance group *Menthol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate        |
|--------|--------------------------|-------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 98.2609 % (> 96.9565 %) |
| Type B | 100.0000 % (> 99.9923 %) | 81.9048 % (> 81.1905 %) |
| Type C | 100.0000 % (> 99.8812 %) | 91.9476 % (> 91.3858 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21443     | 21932               | 2.36                         | 90.57                           |
| 21601     | 21932               | 2.91                         | 89.52                           |
| 21932     | 21932               | 0.00                         | 97.15                           |
| 22657     | 22657               | 0.00                         | 96.62                           |
| 22825     | 22825               | 0.00                         | 85.81                           |
| 23596     | 22825               | 2.08                         | 83.77                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Mepivacaine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20710-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Mepivacaine hydrochloride; Mepivacaini hydrochloridum; Mepivacainum hydrochloricum

### Special notes

When selecting the *Mepivacaine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Mepivacaine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Mepivacaine hydr... | 12A20-N12        | 20710     | 40      | 1401555            |
| Fagron   | Mepivacaine hydr... | 13L04-B07-297077 | 21672     | 40      | AR-15-FG-007876-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Mepivacaine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *Mepivacaine hydrochloride*.

| Supplier | Substance                 | Batch            | Sample ID          | Spectra |
|----------|---------------------------|------------------|--------------------|---------|
| Fagron   | Mepivacaine hydrochloride | 13L04-B07-297077 | 21672 <sup>†</sup> | 20      |
| Fagron   | Mepivacaine hydrochloride | 15I16-B01-322906 | 23212              | 40      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 4 spectra from 4 *Apo-Ident* customers from 3 batches from the substance/substance group *Mepivacaine hydrochloride*.

| Supplier | Substance                 | Batch            | Spectra |
|----------|---------------------------|------------------|---------|
| Fagron   | Mepivacaine hydrochloride | 12E31-B40-305570 | 1       |
| Fagron   | Mepivacaine hydrochloride | 13G05-N02        | 1       |
| Caelo    | Mepivacaine hydrochloride | 13G05-N02        | 1       |
| Fagron   | Mepivacaine hydrochloride | 12F20-N07        | 1       |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Mepivacaine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Mepivacaine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 3             | 1              | 69 629        |

The substance/substance group *Mepivacaine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20710     | 20710               | 0.00                         | 25.12                           |
| 21672     | 21672               | 0.00                         | 26.56                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Labor-

prüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Mesalazine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21772-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Mesalazine; Mesalazinum

### Special notes

When selecting the *Mesalazine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Mesalazine*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate        |
|----------|------------|------------------|-----------|---------|--------------------|
| Euro OTC | Mesalazine | 1206029-04       | 21772     | 40      | AR-15-FG-011819-01 |
| Euro OTC | Mesalazine | 1206029-04       | 21887     | 40      | 20140923           |
| Fagron   | Mesalazine | 15H13-B06-317177 | 22356     | 40      | 20150827           |
| Euro OTC | Mesalazine | 1602005          | 22518     | 40      | 20160218*          |
| Euro OTC | Mesalazine | 1602005-01       | 22925     | 40      | 20160218           |
| Fagron   | Mesalazine | 16I28-B02-327679 | 22929     | 40      | 20161128           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Mesalazine*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 124 spectra of 5 reference samples from the substance/substance group *Mesalazine*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Euro OTC | Mesalazine | 1206029-04       | 21772 <sup>†</sup> | 20      |
| Euro OTC | Mesalazine | 1206029-04       | 21887 <sup>†</sup> | 20      |
| Fagron   | Mesalazine | 15H13-B06-317177 | 22356 <sup>†</sup> | 20      |
| Euro OTC | Mesalazine | 1611019          | 22872              | 40      |
| Fagron   | Mesalazine | 16I28-B02-327679 | not required       | 24      |

- 146 605 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 7 spectra from 3 *Apo-Ident* customers from 4 batches from the substance/substance group *Mesalazine*.

| Supplier | Substance  | Batch            | Spectra |
|----------|------------|------------------|---------|
| Euro OTC | Mesalazine | 1206029-04       | 1       |
| Euro OTC | Mesalazine | 1602005-01       | 2       |
| Euro OTC | Mesalazine | 1602005-02       | 3       |
| Fagron   | Mesalazine | 16128-B02-327679 | 1       |

- 69 626 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Mesalazine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Mesalazine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 124           | 0              | 146 605       |
| <b>Type C</b> | 0              | 6             | 1              | 69 626        |

The substance/substance group *Mesalazine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.1613 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21772     | 21772               | 0.00                         | 70.08                           |
| 21887     | 21772               | 6.24                         | 66.36                           |
| 22356     | 22518               | 6.57                         | 61.67                           |
| 22518     | 22518               | 0.00                         | 59.71                           |
| 22925     | 22518               | 8.67                         | 63.93                           |
| 22929     | 22518               | 9.60                         | 66.48                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | Metamizol sodium monohydrate                                    |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 22634-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Metamizol sodium monohydrate; Metamizolum natricum monohydricum

### Special notes

When selecting the *Metamizol sodium monohydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Metamizol sodium monohydrate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Metamizol sodium... | 161610   | 22634     | 40      | 20160714*   |
| Caelo    | Metamizol sodium... | 15362816 | 22666     | 40      | 20151106    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Metamizol sodium monohydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *Metamizol sodium monohydrate*.

| Supplier | Substance                    | Batch    | Sample ID | Spectra |
|----------|------------------------------|----------|-----------|---------|
| Caelo    | Metamizol sodium monohydrate | 15362815 | 22726     | 40      |
| Caelo    | Metamizol sodium monohydrate | 161610   | 23313     | 40      |

- 146 649 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Metamizol sodium monohydrate*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Metamizol sodium monohydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Metamizol sodium monohydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 77            | 3              | 146 649       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Metamizol sodium monohydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 96.2500 % (> 92.5000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22634     | 22634               | 0.00                         | 46.14                           |
| 22666     | 22634               | 18.03                        | 42.74                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Methacholine chloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20733-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Methacholine chloride; Methacholinii chloridum; Methacholinium chloratum

### Special notes

When selecting the *Methacholine chloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Methacholine chloride*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------------|-----------|-----------|---------|-------------|
| Fagron   | Methacholine chl... | 12F01-N04 | 20733     | 60      | 1403251     |
| Caelo    | Methacholine chl... | 13260303  | 21251     | 40      | 20130827    |
| Caelo    | Methacholine chl... | 13260303  | 21592     | 40      | 20130827    |
| Caelo    | Methacholine chl... | 162293    | 22635     | 40      | 20160815*   |
| Caelo    | Methacholine chl... | 16229304  | 22661     | 40      | 20160815    |

*continued on the next page*

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Caelo    | Methacholine chl... | 16229301         | 22662     | 40      | 20160815    |
| Fagron   | Methacholine chl... | 16L20-B01-329966 | 22976     | 40      | 20170123    |
| Fagron   | Methacholine chl... | 16L20-B01-329968 | 22977     | 40      | 20170123    |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 340 spectra of 8 reference samples from the substance/substance group *Methacholine chloride*. These samples are listed above in the [calibration samples](#) section.
- 71 046 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 580 spectra of 13 reference samples from the substance/substance group *Methacholine chloride*.

| Supplier | Substance             | Batch            | Sample ID          | Spectra |
|----------|-----------------------|------------------|--------------------|---------|
| Caelo    | Methacholine chloride | 13260302         | 21420              | 60      |
| Caelo    | Methacholine chloride | 13260302         | 21590              | 60      |
| Caelo    | Methacholine chloride | 13260303         | 21592 <sup>†</sup> | 20      |
| Caelo    | Methacholine chloride | 163299           | 23049              | 40      |
| Caelo    | Methacholine chloride | 163299           | 23624              | 40      |
| Caelo    | Methacholine chloride | 13260302         | 21420SI            | 60      |
| Caelo    | Methacholine chloride | 13260303         | 21592SI            | 60      |
| Caelo    | Methacholine chloride | 162293           | 22635SI            | 40      |
| Caelo    | Methacholine chloride | 16229304         | 22661SI            | 40      |
| Caelo    | Methacholine chloride | 16229301         | 22662SI            | 40      |
| Fagron   | Methacholine chloride | 16L20-B01-329966 | 22976SI            | 40      |
| Fagron   | Methacholine chloride | 16L20-B01-329968 | 22977SI            | 40      |
| Caelo    | Methacholine chloride | 163299           | 23049SI            | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 149 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 17 spectra from 8 *Apo-Ident* customers from 13 batches from the substance/substance group *Methacholine chloride*.

| Supplier             | Substance             | Batch            | Spectra |
|----------------------|-----------------------|------------------|---------|
| Fagron               | Methacholine chloride | 10031504         | 1       |
| Fagron               | Methacholine chloride | 135000B          | 2       |
| Fagron               | Methacholine chloride | 13/13-N03        | 2       |
| Fagron               | Methacholine chloride | 14G30-B03-296210 | 1       |
| anzag 18.12.14 25,19 | Methacholine chloride | 14G30-B03-296209 | 1       |
| Fagron               | Methacholine chloride | 14K20-B03-300973 | 2       |
| Fagron               | Methacholine chloride | 14G30-B03-296211 | 1       |
| Fagron               | Methacholine chloride | 15F10-B02-315523 | 1       |
| Fagron               | Methacholine chloride | 15F10-B02-315831 | 1       |
| Fagron               | Methacholine chloride | 16L20-B01        | 1       |
| Fagron               | Methacholine chloride | 312160           | 1       |
| Fagron               | Methacholine chloride | 24061503         | 1       |
| Fagron               | Methacholine chloride | 13G10-N05        | 2       |

- 69 616 spectra from 414 *Apo-Ident* customers from a total of 23 788 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Methacholine chloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Methacholine chloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 340           | 0              | 71 046        |
| <b>Type B</b> | 0              | 578           | 2              | 146 149       |
| <b>Type C</b> | 0              | 16            | 1              | 69 616        |

The substance/substance group *Methacholine chloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.2353 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.6552 % (> 99.1379 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20733     | 20733               | 0.00                         | 77.35                           |
| 21251     | 20733               | 6.82                         | 80.73                           |
| 21592     | 20733               | 7.16                         | 70.16                           |
| 22635     | 22635               | 0.00                         | 92.44                           |
| 22661     | 20733               | 9.71                         | 83.84                           |
| 22662     | 22635               | 6.75                         | 91.80                           |
| 22976     | 20733               | 4.82                         | 73.30                           |
| 22977     | 20733               | 8.50                         | 80.22                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Methionine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20971-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Methionine; Methioninum

### Special notes

When selecting the *Methionine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Methionine*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate        |
|----------|------------|------------------|-----------|---------|--------------------|
| Fagron   | Methionine | 12K01-N03        | 20971     | 40      | 1402432            |
| Euro OTC | Methionine | L1404041-01      | 21751     | 40      | 20140508           |
| Fagron   | Methionine | 13L19-B36-295115 | 21786     | 40      | 20140108           |
| Euro OTC | Methionine | 1602012          | 22368     | 40      | 20160219*          |
| Caelo    | Methionine | 15404102         | 22727     | 40      | AR-17-FG-000285-02 |
| Caelo    | Methionine | 16274007         | 23258     | 40      | 20161014           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Methionine*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 6 reference samples from the substance/substance group *Methionine*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Fagron   | Methionine | 11H05-N01        | 20421              | 40      |
| Euro OTC | Methionine | L1404041-01      | 21751 <sup>†</sup> | 20      |
| Fagron   | Methionine | 13L19-B36-295115 | 21786 <sup>†</sup> | 20      |
| Euro OTC | Methionine | 1602012          | 22368 <sup>†</sup> | 20      |
| Euro OTC | Methionine | 1609024          | 22787              | 40      |
| Euro OTC | Methionine | 1703042          | 23126              | 40      |

- 146 549 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 13 spectra from 4 *Apo-Ident* customers from 11 batches from the substance/substance group *Methionine*.

| Supplier | Substance  | Batch            | Spectra |
|----------|------------|------------------|---------|
| Fagron   | Methionine | 13L19-B36        | 2       |
| Fagron   | Methionine | 15A15-B08-307753 | 1       |
| Fagron   | Methionine | 14G31-B02-297517 | 1       |
| Euro OTC | Methionine | L1505001-01      | 1       |
| dr.behr  | Methionine | WE14020068-02    | 1       |
| Fagron   | Methionine | 12D27-N06        | 1       |
| Fagron   | Methionine | 12G27-N01        | 1       |
| Fagron   | Methionine | 12K01-N03        | 2       |
| Fagron   | Methionine | 13G09-N02        | 1       |
| Fagron   | Methionine | 8116020107       | 1       |
| Euro OTC | Methionine | 1602012-01       | 1       |

- 69 620 spectra from 414 *Apo-Ident* customers from a total of 23 790 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Methionine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Methionine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 180           | 0              | 146 549       |
| <b>Type C</b> | 0              | 13            | 0              | 69 620        |

The substance/substance group *Methionine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.6667 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20971     | 20971               | 0.00                         | 58.02                           |
| 21751     | 22368               | 3.14                         | 56.54                           |
| 21786     | 22368               | 3.26                         | 56.99                           |
| 22368     | 22368               | 0.00                         | 55.41                           |
| 22727     | 22727               | 0.00                         | 59.90                           |
| 23258     | 22727               | 5.96                         | 58.56                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Methoxsalen**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20233-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Methoxsalen; Methoxsalenum

### Special notes

When selecting the *Methoxsalen* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Methoxsalen*:

| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate |
|----------|-------------|------------------|-----------|---------|-------------|
| Euro OTC | Methoxsalen | 130604101        | 21555     | 40      | 20130805    |
| Euro OTC | Methoxsalen | 1506013          | 21862     | 40      | 20150706*   |
| Euro OTC | Methoxsalen | 1608019          | 22785     | 40      | 20160913*   |
| Fagron   | Methoxsalen | 15J15-B03-321321 | 23165     | 40      | 20151124    |
| Caelo    | Methoxsalen | 16103003         | 23167     | 40      | 20160415    |
| Caelo    | Methoxsalen | 170781           | 23346     | 40      | 20170427*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Methoxsalen*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 510 spectra of 14 reference samples from the substance/substance group *Methoxsalen*.

| Supplier | Substance   | Batch            | Sample ID          | Spectra |
|----------|-------------|------------------|--------------------|---------|
| Euro OTC | Methoxsalen | 2909040-02       | 20233              | 40      |
| Fagron   | Methoxsalen | 11F21-N02        | 20543              | 40      |
| Euro OTC | Methoxsalen | 130604101        | 21555 <sup>†</sup> | 20      |
| Euro OTC | Methoxsalen | 1506013          | 21862 <sup>†</sup> | 20      |
| Caelo    | Methoxsalen | 16103014         | 23166              | 40      |
| Caelo    | Methoxsalen | 170781           | 23333              | 40      |
| Euro OTC | Methoxsalen | 130604101        | 21555SI            | 55      |
| Euro OTC | Methoxsalen | 1506013          | 21862SI            | 45      |
| Euro OTC | Methoxsalen | 1608019          | 22785SI            | 34      |
| Fagron   | Methoxsalen | 15J15-B03-321321 | 23165SI            | 30      |
| Caelo    | Methoxsalen | 16103014         | 23166SI            | 33      |
| Caelo    | Methoxsalen | 16103003         | 23167SI            | 37      |
| Caelo    | Methoxsalen | 170781           | 23333SI            | 40      |
| Caelo    | Methoxsalen | 170781           | 23346SI            | 36      |

- 146 219 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 106 spectra from 49 *Apo-Ident* customers from 50 batches from the substance/substance group *Methoxsalen*.

| Supplier                   | Substance   | Batch            | Spectra |
|----------------------------|-------------|------------------|---------|
| Caelo                      | Methoxsalen | 1503009-01       | 5       |
| Euro OTC                   | Methoxsalen | 1506013-01       | 7       |
| Caelo                      | Methoxsalen | 11376420         | 2       |
| Caelo                      | Methoxsalen | 11376428         | 1       |
| Caelo                      | Methoxsalen | 11376435         | 1       |
| Caelo                      | Methoxsalen | 11376433         | 1       |
| Audor Pharma               | Methoxsalen | 1203009M         | 1       |
| Euro OTC                   | Methoxsalen | 1306041-01       | 2       |
| Fagron                     | Methoxsalen | 12E02-N05        | 2       |
| PHOENIX 18.02.14           | Methoxsalen | 1306041-01       | 2       |
| Caelo                      | Methoxsalen | 1409003-01       | 5       |
| Euro OTC                   | Methoxsalen | 1409003-01       | 3       |
| Caelo                      | Methoxsalen | 1409003-02       | 1       |
| Euro OTC                   | Methoxsalen | 140900302        | 1       |
| Euro OTC                   | Methoxsalen | 1409003-02       | 2       |
| Fagron                     | Methoxsalen | 14f06-b05-296500 | 1       |
| Fagron                     | Methoxsalen | 14F06-B05-296500 | 1       |
| Fagron                     | Methoxsalen | 14F06-B05-296501 | 2       |
| Caelo                      | Methoxsalen | 14F06-B05-296501 | 1       |
| Phoenix                    | Methoxsalen | 14F06-B05-296502 | 1       |
| Fagron                     | Methoxsalen | 14F06-B05-301978 | 1       |
| Euro OTC                   | Methoxsalen | 1503009-01       | 7       |
| Euro OTC                   | Methoxsalen | 150300901        | 1       |
| Euroo                      | Methoxsalen | 1503009-01       | 1       |
| Euro OTC                   | Methoxsalen | 1503009-02       | 3       |
| Euro OTC                   | Methoxsalen | 1506013-02       | 2       |
| Caelo                      | Methoxsalen | 15244204         | 3       |
| Herbal Creations/Caesar... | Methoxsalen | 15244203         | 1       |
| Herbal Creations/Caesar... | Methoxsalen | 15244205         | 1       |
| Caelo                      | Methoxsalen | 15244205         | 2       |
| Herbal creations/Caesar... | Methoxsalen | 15244208         | 1       |
| Caelo                      | Methoxsalen | 15244209         | 1       |
| Herbal creations/Caesar... | Methoxsalen | 15244212         | 1       |
| Caelo                      | Methoxsalen | 15244216         | 1       |
| Fagron                     | Methoxsalen | 15F23-B03-318166 | 1       |
| Caelo                      | Methoxsalen | 16/079/M         | 1       |
| Euro OTC                   | Methoxsalen | 160801902        | 1       |
| Sanacorp                   | Methoxsalen | 1AKD6            | 1       |
| Fagron                     | Methoxsalen | 2111A-03262      | 2       |
| Audor Pharma               | Methoxsalen | AP15244213M      | 3       |
| Euro OTC                   | Methoxsalen | 1104010-01       | 1       |
| EuRho                      | Methoxsalen | 1104010-01       | 1       |
| Caelo                      | Methoxsalen | 11376401         | 2       |
| Phönix/Maros               | Methoxsalen | 11376408         | 2       |
| Caelo                      | Methoxsalen | 11376413         | 2       |
| Noweda                     | Methoxsalen | 11D07-N16        | 2       |
| Fagron                     | Methoxsalen | 11D07-N16        | 1       |
| Fagron                     | Methoxsalen | 11F21-N02        | 1       |

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| Supplier                  | Substance   | Batch         | Spectra |
|---------------------------|-------------|---------------|---------|
| Fagron                    | Methoxsalen | 11f21-n02     | 1       |
| Euro OTC                  | Methoxsalen | 1203009-01    | 1       |
| Say Phytoceut. Ltd/Noweda | Methoxsalen | 1209015-01    | 4       |
| Euro OTC                  | Methoxsalen | 1209015-01    | 3       |
| Euro OTC                  | Methoxsalen | 120901501     | 1       |
| Fagron                    | Methoxsalen | 12G02-N14     | 1       |
| Fagron                    | Methoxsalen | 13A10N06      | 1       |
| Caelo                     | Methoxsalen | 13c13-n06     | 1       |
| Audor Pharma              | Methoxsalen | AP1011024-01M | 1       |
| Nachprüfung               | Methoxsalen | 4211Q-03262   | 1       |
| Fagron                    | Methoxsalen |               | 1       |
| Fagron                    | Methoxsalen | MS01/13-14    | 1       |

- 69 527 spectra from 414 *Apo-Ident* customers from a total of 23 751 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Methoxsalen* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Methoxsalen* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 433           | 77             | 146 219       |
| <b>Type C</b> | 0              | 105           | 1              | 69 527        |

The substance/substance group *Methoxsalen* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 84.9020 % (> 84.3137 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 99.0566 % (> 96.2264 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.



### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21555     | 21862               | 5.19                         | 77.19                           |
| 21862     | 21862               | 0.00                         | 77.67                           |
| 22785     | 22785               | 0.00                         | 75.95                           |
| 23165     | 22785               | 6.17                         | 73.29                           |
| 23167     | 22785               | 7.57                         | 72.94                           |
| 23346     | 23346               | 0.00                         | 71.91                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Methyl cellulose**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20705-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Methyl cellulose; Hypromellose 4000; Hypromellosem E4M Prem; Methylcellulosum; Methylhydroxypropylcellulosum E4M Prem

### Special notes

When selecting the *Methyl cellulose* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Methyl cellulose*:

| Supplier | Substance         | Batch            | Sample ID | Spectra | Certificate |
|----------|-------------------|------------------|-----------|---------|-------------|
| Fagron   | Methyl cellulose  | 12D02-N09        | 20705     | 40      | 1402447     |
| Caelo    | Hypromellose 4000 | 13155006         | 20919     | 40      | 1402056     |
| Caelo    | Methyl cellulose  | 13130115         | 21570     | 40      | 20130517    |
| Caelo    | Hypromellose 4000 | 14338801         | 21702     | 30      | 20141217    |
| Caelo    | Methyl cellulose  | 160602           | 22457     | 40      | 20160323*   |
| Fagron   | Hypromellose 4000 | 15G08-B14-314845 | 22609     | 40      | 20150727    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 230 spectra of 6 reference samples from the substance/substance group *Methyl cellulose*. These samples are listed above in the [calibration samples](#) section.
- 71 156 spectra from a total of 1546 batches from further 373 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 335 spectra of 10 reference samples from the substance/substance group *Methyl cellulose*.

| Supplier | Substance         | Batch            | Sample ID          | Spectra |
|----------|-------------------|------------------|--------------------|---------|
| Fagron   | Hypromellose 4000 | 11A27-N27        | 20222              | 40      |
| Caelo    | Methyl cellulose  | 10247609         | 20225              | 40      |
| Caelo    | Hypromellose 4000 | 13155006         | 20931              | 40      |
| Caelo    | Methyl cellulose  | 13130115         | 21570 <sup>†</sup> | 20      |
| Caelo    | Hypromellose 4000 | 14338801         | 21702 <sup>†</sup> | 15      |
| Caelo    | Methyl cellulose  | 160602           | 22457 <sup>†</sup> | 20      |
| Caelo    | Hypromellose 4000 | 162244           | 22757              | 40      |
| Fagron   | Methyl cellulose  | 15H04-B07-331291 | 23224              | 40      |
| Caelo    | Hypromellose 4000 | 171150           | 23284              | 40      |
| Caelo    | Methyl cellulose  | 171704           | 23627              | 40      |

- 146 394 spectra from a total of 3184 batches from further 861 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 248 spectra from 132 *Apo-Ident* customers from 110 batches from the substance/substance group *Methyl cellulose*.

| Supplier                   | Substance         | Batch            | Spectra |
|----------------------------|-------------------|------------------|---------|
| Caelo                      | Hypromellose 4000 | 12239502         | 1       |
| Euro OTC                   | Hypromellose 4000 | 1306022-02       | 1       |
| Caelo                      | Hypromellose 4000 | 13155004         | 10      |
| Fagron                     | Hypromellose 4000 | 13D03-N03        | 7       |
| Fagron                     | Hypromellose 4000 | 13E02-B03-290531 | 3       |
| Fagron                     | Hypromellose 4000 | 13H09-N04        | 11      |
| Caelo                      | Hypromellose 4000 | 14338801         | 1       |
| Caelo                      | Hypromellose 4000 | 14338802         | 1       |
| Caelo                      | Hypromellose 4000 | 14338803         | 1       |
| Caelo                      | Hypromellose 4000 | 1438801          | 1       |
| Fagron                     | Hypromellose 4000 | 14C05B03         | 1       |
| Fagron                     | Hypromellose 4000 | 14C05-B03-294708 | 6       |
| DOW Chemical Company Mi... | Hypromellose 4000 | 14G02-B11-296850 | 1       |
| Phönix Gotha               | Hypromellose 4000 | 14G02-B11-296850 | 1       |
| Fagron                     | Hypromellose 4000 | 14G02-B11-296850 | 1       |
| Fagron                     | Hypromellose 4000 | 14G02-B11-296851 | 1       |
| Fagron                     | Hypromellose 4000 | 14G02-B11-302118 | 2       |
| Fagron                     | Hypromellose 4000 | 15B02-B05        | 1       |
| Caelo                      | Hypromellose 4000 | 15B02-B05-308852 | 1       |
| Fagron                     | Hypromellose 4000 | 15B02-B05-308852 | 1       |
| Fagron                     | Hypromellose 4000 | 15G08-B14-310845 | 4       |
| Fagron                     | Hypromellose 4000 | 15g08-b14-310845 | 2       |
| Fagron                     | Hypromellose 4000 | 15G08-B14-314845 | 4       |
| Caelo                      | Hypromellose 4000 | 16224401         | 4       |
| Caelo                      | Hypromellose 4000 | 16224403         | 1       |
| Caelo                      | Hypromellose 4000 | 16224407         | 1       |
| Caelo                      | Hypromellose 4000 | 16224409         | 1       |
| Fagron                     | Hypromellose 4000 | 16B16B07         | 1       |
| FRAGON/Poenix              | Hypromellose 4000 | 16B16-B07-18276  | 1       |
| Fagron                     | Hypromellose 4000 | 16B16-B07-318531 | 2       |
| Fagron                     | Hypromellose 4000 | 16H23-B02-332066 | 2       |
| Fagron                     | Hypromellose 4000 | 16B16-B07-321327 | 1       |
| Fagron                     | Hypromellose 4000 | 1K01012N11       | 1       |
| Fagron                     | Hypromellose 4000 | 700182-0001      | 1       |
| Fagron                     | Hypromellose 4000 | 11H26-N01        | 1       |
| Caelo                      | Hypromellose 4000 | 12098702         | 1       |
| Kehr                       | Hypromellose 4000 | 12098704         | 1       |
| Caelo                      | Hypromellose 4000 | 12215504         | 2       |
| Fagron                     | Hypromellose 4000 | 12E02-N03        | 2       |
| Fagron                     | Hypromellose 4000 | 12A30-N02        | 3       |
| Fagron                     | Hypromellose 4000 | 12G23-N03        | 2       |
| Caelo                      | Hypromellose 4000 | 13100304         | 3       |
| Caelo                      | Hypromellose 4000 | 13155005         | 1       |
| Noweda                     | Hypromellose 4000 | 1315505          | 1       |
| Fagron                     | Hypromellose 4000 | 13D03N03         | 1       |
| Fagron                     | Hypromellose 4000 | 1J31012N11       | 3       |
| Caelo                      | Hypromellose 4000 | ZH19012N12       | 2       |
| Fagron                     | Hypromellose 4000 | ZH19012N12       | 2       |
| Fagron                     | Hypromellose 4000 | 10G09-N03        | 1       |
| Fagron                     | Hypromellose 4000 | 13E02-B03-290532 | 1       |
| Caelo                      | Methyl cellulose  | 5081404          | 1       |
| Fagron                     | Methyl cellulose  | 12H06-N06        | 2       |

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| <b>Supplier</b>            | <b>Substance</b>  | <b>Batch</b>      | <b>Spectra</b> |
|----------------------------|-------------------|-------------------|----------------|
| Fagron                     | Methyl cellulose  | 13/26-N04         | 1              |
| Caelo                      | Methyl cellulose  | 12L05-N03         | 1              |
| Caelo                      | Methyl cellulose  | 13130104          | 5              |
| Caelo                      | Methyl cellulose  | 13130109          | 5              |
| Fagron                     | Methyl cellulose  | 131301(09)        | 1              |
| Caelo                      | Methyl cellulose  | 13130115          | 6              |
| Caelo                      | Methyl cellulose  | 13130121          | 3              |
| Fagron                     | Methyl cellulose  | 13E02-B03-290531  | 1              |
| Caelo                      | Methyl cellulose  | 14197502          | 4              |
| Caelo                      | Methyl cellulose  | 14197513          | 1              |
| Vdl nachliefer; 2.7.15;... | Methyl cellulose  | 14197502          | 1              |
| Caelo                      | Methyl cellulose  | 14197514          | 6              |
| Caelo                      | Methyl cellulose  | 15179602          | 10             |
| Euro OTC                   | Methyl cellulose  | 15179602          | 1              |
| Caelo                      | Methyl cellulose  | 15179605          | 7              |
| Fagron                     | Methyl cellulose  | 15G08B14314845    | 1              |
| Caelo                      | Methyl cellulose  | 16060202          | 1              |
| Caelo                      | Methyl cellulose  | 16060206          | 3              |
| Caelo                      | Methyl cellulose  | 16060210          | 4              |
| Caelo                      | Methyl cellulose  | 12044931          | 2              |
| Caelo                      | Methyl cellulose  | 13021401          | 1              |
| Caelo                      | Methyl cellulose  | 13130102          | 1              |
| Caelo                      | Methyl cellulose  | 20021401          | 1              |
| Caelo                      | Methyl cellulose  | 10247604          | 1              |
| Euro OTC                   | Methyl cellulose  | 10247609          | 1              |
| Caelo                      | Methyl cellulose  | 11127303          | 1              |
| Caelo                      | Methyl cellulose  | 11127314          | 1              |
| Fagron                     | Methyl cellulose  | 11G15-N08         | 1              |
| Caelo                      | Methyl cellulose  | 12044903          | 3              |
| Caelo                      | Methyl cellulose  | 12044907          | 2              |
| Caelo                      | Methyl cellulose  | 12044917          | 1              |
| Caelo                      | Methyl cellulose  | 12044918          | 2              |
| Caelo                      | Methyl cellulose  | 12044922          | 3              |
| Caesar & Loretz GmbH       | Methyl cellulose  | 12044922          | 1              |
| Caelo                      | Methyl cellulose  | 12044927          | 6              |
| Euro OTC                   | Methyl cellulose  | 12044927          | 1              |
| Nachprüfung 2609           | Hypromellose 4000 | 11H26-N01         | 1              |
| Fagron                     | Hypromellose 4000 | 14G02-B11         | 2              |
| Gehe                       | Hypromellose 4000 | 14G02-B11         | 1              |
| Fagron                     | Hypromellose 4000 | 14g02-b11-302118  | 2              |
| Fagron                     | Hypromellose 4000 | 14G02-B11-302121  | 1              |
| Fagron                     | Hypromellose 4000 | 15G08-B14         | 1              |
| Jenne                      | Hypromellose 4000 | 15G08-B14         | 1              |
| Fagron                     | Hypromellose 4000 | 15G08B14314185    | 2              |
| Fagron                     | Hypromellose 4000 | 15g08-b14-314845  | 1              |
| Fagron                     | Hypromellose 4000 | 16B16-B07-318276  | 1              |
| Phoenix                    | Hypromellose 4000 | 16B16-B07         | 1              |
| Fagron                     | Hypromellose 4000 | 16B-16-B07-321327 | 1              |
| Fagron                     | Hypromellose 4000 | 3G08012N11        | 1              |
| Gehe / 26.10.12 Fragon     | Hypromellose 4000 | 9D30-N05          | 1              |
| Fagron                     | Hypromellose 4000 | D180F8Q011        | 1              |
| Gehe                       | Hypromellose 4000 | 11D15-N06         | 1              |
| Caelo                      | Hypromellose 4000 | D180F8Q011        | 1              |
| Anzag am 03.05.2012        | Hypromellose 4000 | 11H26-N01         | 1              |
| anzag, 21.11.2012          | Hypromellose 4000 | 12E02-N03         | 3              |
| Fagron                     | Hypromellose 4000 | 12D03-N03         | 1              |
| Gehe                       | Hypromellose 4000 | 12E02-N03         | 1              |
| Caelo                      | Hypromellose 4000 | 13155002          | 1              |
| Fagron                     | Hypromellose 4000 | 12H20-N05         | 1              |
| Fagron                     | Hypromellose 4000 | 12G23-N03         | 1              |

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| Supplier                   | Substance         | Batch            | Spectra |
|----------------------------|-------------------|------------------|---------|
| Caelo                      | Hypromellose 4000 | 13D03-N03        | 1       |
| Caelo                      | Hypromellose 4000 | 13d03-n03        | 1       |
| Phoenix                    | Hypromellose 4000 | 13E02-B03        | 1       |
| Fagron                     | Hypromellose 4000 | 13h09-m04        | 1       |
| Alliance Health 27.12.2... | Hypromellose 4000 | 13D03-N03        | 1       |
| Phonix                     | Hypromellose 4000 | 13H09-N04        | 1       |
| Fagron                     | Hypromellose 4000 | 14C05-B03        | 1       |
| Gatt-Koller / Phoenix      | Hypromellose 4000 | 14C05-B03-291647 | 2       |
| Phoenix                    | Hypromellose 4000 | 14c05-b03-294708 | 1       |
| Fagron                     | Hypromellose 4000 | 1A01012N11       | 1       |
| Fagron                     | Hypromellose 4000 | 20110612-2       | 1       |
| Fagron                     | Hypromellose 4000 | YI16012N11       | 1       |
| Fagron                     | Hypromellose 4000 | 13H08-N04        | 2       |
| Fagron                     | Hypromellose 4000 | 14c05-B03-294708 | 1       |
| Caelo                      | Hypromellose 4000 | 14C05-B03-294708 | 1       |
| Fagron                     | Hypromellose 4000 | 14C05-B03-294711 | 1       |
| Fagron                     | Hypromellose 4000 | 2H12012N12       | 1       |

- 69 385 spectra from 414 *Apo-Ident* customers from a total of 23 693 batches from a further 695 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Methyl cellulose* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Methyl cellulose* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 230           | 0              | 71 156        |
| <b>Type B</b> | 0              | 334           | 1              | 146 394       |
| <b>Type C</b> | 0              | 239           | 9              | 69 385        |

The substance/substance group *Methyl cellulose* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.3913 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.7015 % (> 98.8060 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 96.3710 % (> 95.1613 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20705     | 20705               | 0.00                         | 30.11                           |
| 20919     | 20919               | 0.00                         | 48.31                           |
| 21570     | 20705               | 10.57                        | 31.07                           |
| 21702     | 20919               | 6.98                         | 49.95                           |
| 22457     | 22457               | 0.00                         | 36.97                           |
| 22609     | 20705               | 11.74                        | 40.96                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Methyl-4-hydroxybenzoate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20345-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Methyl-4-hydroxybenzoate; Methylis parahydroxybenzoas; Methylum parahydroxybenzoicum

### Special notes

When selecting the *Methyl-4-hydroxybenzoate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Methyl-4-hydroxybenzoate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Caelo    | Methyl-4-hydroxy... | 11090034         | 20693     | 40      | 20110428    |
| Euro OTC | Methyl-4-hydroxy... | 1205025-01       | 20697     | 40      | 20120601    |
| Euro OTC | Methyl-4-hydroxy... | 1601037          | 22305     | 40      | 20160119*   |
| Fagron   | Methyl-4-hydroxy... | 14L30-T01-018345 | 23223     | 40      | 20150309    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Methyl-4-hydroxybenzoate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 320 spectra of 8 reference samples from the substance/substance group *Methyl-4-hydroxybenzoate*.

| Supplier | Substance                | Batch    | Sample ID          | Spectra |
|----------|--------------------------|----------|--------------------|---------|
| Caelo    | Methyl-4-hydroxybenzoate | 10039706 | 20134              | 40      |
| Caelo    | Methyl-4-hydroxybenzoate | 9344712  | 20345              | 40      |
| Caelo    | Methyl-4-hydroxybenzoate | 11090031 | 20505              | 40      |
| Caelo    | Methyl-4-hydroxybenzoate | 13268813 | 21439              | 60      |
| Euro OTC | Methyl-4-hydroxybenzoate | 1601037  | 22305 <sup>†</sup> | 20      |
| Caelo    | Methyl-4-hydroxybenzoate | 15063820 | 23216              | 40      |
| Caelo    | Methyl-4-hydroxybenzoate | 171581   | 23317              | 40      |
| Euro OTC | Methyl-4-hydroxybenzoate | 1706005  | 23703              | 40      |

- 146 409 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 196 spectra from 117 *Apo-Ident* customers from 83 batches from the substance/substance group *Methyl-4-hydroxybenzoate*.

| Supplier             | Substance                | Batch         | Spectra |
|----------------------|--------------------------|---------------|---------|
| Caelo                | Methyl-4-hydroxybenzoate | 13268809      | 8       |
| Caelo                | Methyl-4-hydroxybenzoate | 6091402       | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 11090031      | 5       |
| Caelo                | Methyl-4-hydroxybenzoate | 12251624      | 7       |
| EuRho                | Methyl-4-hydroxybenzoate | 110403101     | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 12081502      | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 13268803      | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 13268802      | 2       |
| Caelo                | Methyl-4-hydroxybenzoate | 13268804      | 6       |
| Caesar & Loretz GmbH | Methyl-4-hydroxybenzoate | 13268809      | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 13268813      | 7       |
| Caelo                | Methyl-4-hydroxybenzoate | 13268821      | 2       |
| Caelo                | Methyl-4-hydroxybenzoate | 13268819      | 1       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 1401027-02    | 2       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 1401027-01    | 1       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 140600501     | 1       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 1406005-01    | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 14120208      | 3       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 1502009-01    | 5       |
| Caelo                | Methyl-4-hydroxybenzoate | 15063802      | 4       |
| Caelo                | Methyl-4-hydroxybenzoate | 15063803      | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 15063806      | 7       |
| Caelo                | Methyl-4-hydroxybenzoate | 15063813      | 2       |
| Caesar/Noweda        | Methyl-4-hydroxybenzoate | 15063806      | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 15063818      | 1       |
| PHÖNIX               | Methyl-4-hydroxybenzoate | 15063819      | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 15063820      | 2       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 1507042-01    | 9       |
| Caelo                | Methyl-4-hydroxybenzoate | 15222203      | 2       |
| Caelo                | Methyl-4-hydroxybenzoate | 15298102      | 10      |
| Caelo                | Methyl-4-hydroxybenzoate | 15298101      | 1       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 1507042-02    | 1       |
| Sanacorp             | Methyl-4-hydroxybenzoate | 15298102      | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 15444916      | 1       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 1601037-01    | 6       |
| Caelo                | Methyl-4-hydroxybenzoate | 413051/1      | 1       |
| GATT-KOLLER/PHOENIX  | Methyl-4-hydroxybenzoate | 6112/01142814 | 1       |
| Phönix               | Methyl-4-hydroxybenzoate | 2AKD3         | 1       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 4314U-01930   | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 713Q-01930    | 1       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 3115M-01930   | 1       |
| Euro OTC             | Methyl-4-hydroxybenzoate | 4312I-01930   | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 8121-01930    | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 9011303       | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 10039706      | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 1009022-01    | 2       |
| Fagron               | Methyl-4-hydroxybenzoate |               | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 10113609      | 1       |
| Eigenherstellung     | Methyl-4-hydroxybenzoate | 100912PML01   | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 1108211930    | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 110900029     | 1       |
| Caelo                | Methyl-4-hydroxybenzoate | 11090030      | 3       |
| Caelo                | Methyl-4-hydroxybenzoate | 11090003      | 1       |
| Gehe                 | Methyl-4-hydroxybenzoate | 11090020      | 1       |

*continued on the next page*

continued from previous page

| Supplier                   | Substance                | Batch       | Spectra |
|----------------------------|--------------------------|-------------|---------|
| Gehe                       | Methyl-4-hydroxybenzoate | 11090031    | 1       |
| Euro OTC                   | Methyl-4-hydroxybenzoate | 1110033-01  | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 11345115    | 10      |
| Post-Apotheke              | Methyl-4-hydroxybenzoate | 1110033-01  | 1       |
| Anzag                      | Methyl-4-hydroxybenzoate | 11345115    | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 111003301   | 1       |
| Noweda                     | Methyl-4-hydroxybenzoate | 11345115    | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 11345120    | 5       |
| Caelo                      | Methyl-4-hydroxybenzoate | 12042202    | 1       |
| phönix, 13.12.2012         | Methyl-4-hydroxybenzoate | 1205025-01  | 1       |
| Euro OTC                   | Methyl-4-hydroxybenzoate | 1212011-01  | 4       |
| Caelo                      | Methyl-4-hydroxybenzoate | 12251605    | 5       |
| Bombastus                  | Methyl-4-hydroxybenzoate | 1212011-01  | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 12251611    | 1       |
| AHD                        | Methyl-4-hydroxybenzoate | 12251624    | 1       |
| Phönix 14.01.2014          | Methyl-4-hydroxybenzoate | 12251624    | 1       |
| PHOENIX am 15.01.2014      | Methyl-4-hydroxybenzoate | 12251624    | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 1251624     | 1       |
| Caesar&lorenz,Phoenix      | Methyl-4-hydroxybenzoate | 13268821    | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 13081308    | 1       |
| Fagron                     | Methyl-4-hydroxybenzoate | 12D18-N01   | 1       |
| Fagron                     | Methyl-4-hydroxybenzoate | 12H02-N08   | 2       |
| Fagron                     | Methyl-4-hydroxybenzoate | 13B25-N03   | 2       |
| Euro OTC                   | Methyl-4-hydroxybenzoate | 172620      | 1       |
| Fagron                     | Methyl-4-hydroxybenzoate | 13E27-N09   | 1       |
| Anzag/                     | Methyl-4-hydroxybenzoate | 201111251   | 1       |
| Fagron                     | Methyl-4-hydroxybenzoate | 20111125-1  | 1       |
| Euro OTC                   | Methyl-4-hydroxybenzoate | 2606022     | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 290114PML01 | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 14120210    | 1       |
| Noweda                     | Methyl-4-hydroxybenzoate | 11090021    | 1       |
| Noweda                     | Methyl-4-hydroxybenzoate | 11090002    | 2       |
| Sanacorp, 12.08.2016, 4... | Methyl-4-hydroxybenzoate | 15298102    | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 12251619    | 2       |
| Fagron                     | Methyl-4-hydroxybenzoate | 12D18N01    | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 13268815    | 1       |
| Noweda                     | Methyl-4-hydroxybenzoate | 21022111/1  | 1       |
| Euro OTC                   | Methyl-4-hydroxybenzoate | 120502501   | 1       |
| Dorfmeister                | Methyl-4-hydroxybenzoate | 1212011-01  | 1       |
| Caelo                      | Methyl-4-hydroxybenzoate | 1225164     | 1       |
| Noweda                     | Methyl-4-hydroxybenzoate | 10113607    | 1       |
| Noweda                     | Methyl-4-hydroxybenzoate | 11090010    | 1       |
| Noweda                     | Methyl-4-hydroxybenzoate | 11090030    | 1       |
| phönix 4.12.2013           | Methyl-4-hydroxybenzoate | 1212011/01  | 1       |

- 69 437 spectra from 414 *Apo-Ident* customers from a total of 23 720 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Methyl-4-hydroxybenzoate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Methyl-4-hydroxybenzoate*

and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 310           | 10             | 146 409       |
| <b>Type C</b> | 0              | 191           | 5              | 69 437        |

The substance/substance group *Methyl-4-hydroxybenzoate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 96.8750 % (> 95.9375 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 97.4490 % (> 95.9184 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20693     | 22305               | 7.60                         | 47.16                           |
| 20697     | 22305               | 6.99                         | 47.04                           |
| 22305     | 22305               | 0.00                         | 46.64                           |
| 23223     | 22305               | 8.34                         | 46.28                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Methylcobalamin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20743-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Methylcobalamin

### Special notes

When selecting the *Methylcobalamin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Methylcobalamin*:

| Supplier | Substance       | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------------|------------|-----------|---------|-------------|
| Euro OTC | Methylcobalamin | 1207019-01 | 20743     | 40      | 1402501     |
| Euro OTC | Methylcobalamin | 1401032-01 | 21721     | 40      | 8778        |
| Euro OTC | Methylcobalamin | 1510002    | 22234     | 40      | 20151201*   |
| Euro OTC | Methylcobalamin | 1401032    | 22239     | 40      | 20151201*   |
| Euro OTC | Methylcobalamin | 1601043    | 22379     | 40      | 20160209*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Methylcobalamin*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 5 reference samples from the substance/substance group *Methylcobalamin*.

| Supplier                   | Substance       | Batch      | Sample ID          | Spectra |
|----------------------------|-----------------|------------|--------------------|---------|
| Hebei Welcome Pharmaceu... | Methylcobalamin | 3090510    | 20438              | 40      |
| Euro OTC                   | Methylcobalamin | 1401032-01 | 21721 <sup>†</sup> | 20      |
| Euro OTC                   | Methylcobalamin | 1510002    | 22234 <sup>†</sup> | 20      |
| Euro OTC                   | Methylcobalamin | 1401032    | 22239 <sup>†</sup> | 20      |
| Euro OTC                   | Methylcobalamin | 1601043    | 22379 <sup>†</sup> | 20      |

- 146 609 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 4 spectra from 2 *Apo-Ident* customers from 4 batches from the substance/substance group *Methylcobalamin*.

| Supplier | Substance       | Batch        | Spectra |
|----------|-----------------|--------------|---------|
| Euro OTC | Methylcobalamin | 1409017-01   | 1       |
| Euro OTC | Methylcobalamin | 1207019-01   | 1       |
| Euro OTC | Methylcobalamin | 1310014-01   | 1       |
| Euro OTC | Methylcobalamin | Ch1207019-01 | 1       |

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Methylcobalamin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Methylcobalamin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 80            | 40             | 146 609       |
| <b>Type C</b> | 0              | 3             | 1              | 69 629        |

The substance/substance group *Methylcobalamin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 66.6667 % (> 64.1667 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20743     | 20743               | 0.00                         | 28.30                           |
| 21721     | 21721               | 0.00                         | 21.73                           |
| 22234     | 22234               | 0.00                         | 28.29                           |
| 22239     | 22239               | 0.00                         | 29.45                           |
| 22379     | 22379               | 0.00                         | 24.67                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Methylprednisolone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20953-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Methylprednisolone; Methylprednisolonum

### Special notes

When selecting the *Methylprednisolone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Methylprednisolone*:

| Supplier | Substance          | Batch            | Sample ID | Spectra | Certificate        |
|----------|--------------------|------------------|-----------|---------|--------------------|
| Fagron   | Methylprednisolone | 13G19-N05        | 20953     | 40      | 1402438            |
| Fagron   | Methylprednisolone | 15I04-B05-311572 | 22275     | 30      | AR-16-FG-009102-01 |
| Fagron   | Methylprednisolone | 15I04-B05-311572 | 22354     | 30      | 20151026           |
| Fagron   | Methylprednisolone | 15I04-B05-311572 | 22275SI   | 30      | AR-16-FG-009102-01 |
| Fagron   | Methylprednisolone | 15I04-B05-311572 | 22354SI   | 30      | 20151026           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 5 reference samples from the substance/substance group *Methylprednisolone*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 170 spectra of 7 reference samples from the substance/substance group *Methylprednisolone*.

| Supplier | Substance          | Batch            | Sample ID            | Spectra |
|----------|--------------------|------------------|----------------------|---------|
| Fagron   | Methylprednisolone | 12D17-N04        | 20650                | 40      |
| Fagron   | Methylprednisolone | 15I04-B05-311572 | 22275 <sup>†</sup>   | 15      |
| Fagron   | Methylprednisolone | 15I04-B05-311572 | 22354 <sup>†</sup>   | 15      |
| Fagron   | Methylprednisolone | 15L15-B01-321887 | 23229                | 40      |
| Fagron   | Methylprednisolone | 15I04-B05-311572 | 22275SI <sup>†</sup> | 15      |
| Fagron   | Methylprednisolone | 15I04-B05-311572 | 22354SI <sup>†</sup> | 15      |
| Fagron   | Methylprednisolone | 15L15-B01-321887 | 23229SI              | 30      |

- 146 559 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Methylprednisolone*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance          | Batch     | Spectra |
|----------|--------------------|-----------|---------|
| Fagron   | Methylprednisolone | 12D17-N04 | 1       |

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Methylprednisolone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Methylprednisolone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 163           | 7              | 146 559       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Methylprednisolone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 95.8824 % (> 94.1176 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20953     | 20953               | 0.00                         | 30.28                           |
| 22275     | 22275               | 0.00                         | 31.94                           |
| 22354     | 22275               | 3.14                         | 32.04                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | Metoclopramide hydrochloride                                    |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 21662-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Metoclopramide hydrochloride; Metoclopramidi hydrochloridum; Metoclopramidum hydrochloricum monohydricum

### Special notes

When selecting the *Metoclopramide hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                            |
|-------------------|------------------------------------------------------------|
| 978-3-7692-5416-7 | European Pharmacopoeia 8th Edition, Basic Version 2014 [3] |
| Komm2.2.40        | Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident [4]          |
| AA004             | Erstellung und Validierung eines IdentModul-Updates        |
| Anhang F          | Zusatz zu den Modellen der zweiten Stufe                   |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Metoclopramide hydrochloride*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate        |
|----------|---------------------|----------|-----------|---------|--------------------|
| Caelo    | Metoclopramide h... | 14193102 | 21662     | 40      | AR-15-FG-002889-01 |
| Caelo    | Metoclopramide h... | 14193102 | 21746     | 40      | 20140725           |
| Caelo    | Metoclopramide h... | 15421101 | 23234     | 40      | 20160226           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Metoclopramide hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 40 spectra of 2 reference samples from the substance/substance group *Metoclopramide hydrochloride*.

| Supplier | Substance                    | Batch    | Sample ID          | Spectra |
|----------|------------------------------|----------|--------------------|---------|
| Caelo    | Metoclopramide hydrochloride | 14193102 | 21662 <sup>†</sup> | 20      |
| Caelo    | Metoclopramide hydrochloride | 14193102 | 21746 <sup>†</sup> | 20      |

- 146 689 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 12 spectra from 12 *Apo-Ident* customers from 3 batches from the substance/substance group *Metoclopramide hydrochloride*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier              | Substance                    | Batch        | Spectra |
|-----------------------|------------------------------|--------------|---------|
| Caelo                 | Metoclopramide hydrochloride | 15227001     | 9       |
| Caesar&loretz,Phoenix | Metoclopramide hydrochloride | 14193101     | 1       |
| Caelo                 | Metoclopramide hydrochloride | 14193101     | 1       |
| Caelo                 | Metoclopramide hydrochloride | 3414U-018969 | 1       |

- 69 621 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Metoclopramide hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Metoclopramide hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 40            | 0              | 146 689       |
| <b>Type C</b> | 0              | 12            | 0              | 69 621        |

The substance/substance group *Metoclopramide hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 85.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21662     | 21662               | 0.00                         | 59.73                           |
| 21746     | 21662               | 3.98                         | 60.62                           |
| 23234     | 21662               | 4.95                         | 62.08                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Metoprolol tartrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21753-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Metoprolol tartrate; Metoprololi tartras

### Special notes

When selecting the *Metoprolol tartrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Metoprolol tartrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Inresa   | Metoprolol tartr... | 309905RII        | 21753     | 40      | AR-15-FG-006635-01 |
| Inresa   | Metoprolol tartr... | 405005RII        | 21805     | 40      | 20140430           |
| Fagron   | Metoprolol tartr... | 16E31-B03-327107 | 22944     | 40      | 20160627           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Metoprolol tartrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 183 spectra of 6 reference samples from the substance/substance group *Metoprolol tartrate*.

| Supplier | Substance           | Batch               | Sample ID          | Spectra |
|----------|---------------------|---------------------|--------------------|---------|
| Inresa   | Metoprolol tartrate | 309905RII           | 21753 <sup>†</sup> | 20      |
| Inresa   | Metoprolol tartrate | 405005RII           | 21805 <sup>†</sup> | 20      |
| Inresa   | Metoprolol tartrate | 405005RIIC/29082016 | 22908              | 40      |
| Fagron   | Metoprolol tartrate | 16E31-B03-327107    | 22927              | 40      |
| Fagron   | Metoprolol tartrate | 16E31-B03-327107    | 22943              | 40      |
| Fagron   | Metoprolol tartrate | 16E31-B03-327107    | not required       | 23      |

- 146 546 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 9 spectra from 4 *Apo-Ident* customers from 6 batches from the substance/substance group *Metoprolol tartrate*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                 | Substance           | Batch       | Spectra |
|--------------------------|---------------------|-------------|---------|
| Antares                  | Metoprolol tartrate | 1014Q-07308 | 1       |
| Inresa                   | Metoprolol tartrate | 4050005RIIB | 1       |
| Th. Geyer                | Metoprolol tartrate | 56392-17-7  | 1       |
| Andor                    | Metoprolol tartrate | APMTP0117MT | 1       |
| Sigma-Aldrich GmbH       | Metoprolol tartrate | LRAA6905    | 4       |
| Sigma Adrich/Alliance H. | Metoprolol tartrate | PHR1076     | 1       |

- 69 624 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Metoprolol tartrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Metoprolol tartrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 183           | 0              | 146 546       |
| <b>Type C</b> | 0              | 9             | 0              | 69 624        |

The substance/substance group *Metoprolol tartrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.7213 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21753     | 21753               | 0.00                         | 58.76                           |
| 21805     | 21753               | 2.70                         | 57.44                           |
| 22944     | 21753               | 12.36                        | 66.23                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Metronidazole**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20001-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Metronidazole; Metronidazolum

### Special notes

When selecting the *Metronidazole* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Metronidazole*:

| Supplier | Substance     | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------|------------|-----------|---------|-------------|
| Caelo    | Metronidazole | 12110410   | 20857     | 40      | 20120515    |
| Fagron   | Metronidazole | 13D10-N02  | 21212     | 40      | 20130516    |
| Euro OTC | Metronidazole | 1212030-02 | 21213     | 40      | 20130627    |
| Caelo    | Metronidazole | 13095007   | 21356     | 40      | 20130426    |
| Euro OTC | Metronidazole | 1508004    | 21881     | 40      | 20150819*   |
| Caelo    | Metronidazole | 160892     | 22472     | 40      | 20160413*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Metronidazole*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 370 spectra of 11 reference samples from the substance/substance group *Metronidazole*.

| Supplier | Substance     | Batch            | Sample ID          | Spectra |
|----------|---------------|------------------|--------------------|---------|
| Caelo    | Metronidazole | 81604189         | 20001              | 30      |
| Caelo    | Metronidazole | 13095005         | 21214              | 40      |
| Caelo    | Metronidazole | 13095007         | 21360              | 40      |
| Euro OTC | Metronidazole | 1508004          | 21881 <sup>†</sup> | 20      |
| Caelo    | Metronidazole | 160892           | 22472 <sup>†</sup> | 20      |
| Euro OTC | Metronidazole | 1609028          | 22751              | 40      |
| Fagron   | Metronidazole | 16I19-B04-326155 | 22835              | 40      |
| Euro OTC | Metronidazole | 1612013          | 22917              | 40      |
| Euro OTC | Metronidazole | 1701039          | 23132              | 40      |
| Euro OTC | Metronidazole | 1707008          | 23542              | 30      |
| Euro OTC | Metronidazole | 1706022          | 23550              | 30      |

- 146 359 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1387 spectra from 315 *Apo-Ident* customers from 358 batches from the substance/substance group *Metronidazole*.

| Supplier                   | Substance     | Batch            | Spectra |
|----------------------------|---------------|------------------|---------|
| Euro OTC                   | Metronidazole | 1307042-01       | 7       |
| Fagron                     | Metronidazole | 1220141155F      | 2       |
| Caelo                      | Metronidazole | 2022015B         | 1       |
| Caelo                      | Metronidazole | 9715621          | 1       |
| Caelo                      | Metronidazole | 7071405          | 1       |
| Caelo                      | Metronidazole | 7031401          | 1       |
| Euro OTC                   | Metronidazole | 10800401         | 1       |
| Caelo                      | Metronidazole | 12081507         | 1       |
| Caelo                      | Metronidazole | 113214021        | 1       |
| Caelo                      | Metronidazole | 11F15-N07        | 1       |
| Caelo                      | Metronidazole | 12091403         | 1       |
| Euro OTC                   | Metronidazole | 121001-02        | 3       |
| Euro OTC                   | Metronidazole | 1212001-02       | 17      |
| Euro OTC                   | Metronidazole | 121030-01        | 1       |
| Corden Pharma              | Metronidazole | 1212001-02       | 2       |
| Dorfmeister                | Metronidazole | 1212030-02       | 1       |
| Euro OTC                   | Metronidazole | 1212030-02       | 7       |
| Caelo                      | Metronidazole | 1212030-01       | 2       |
| Gehe am 04.02.14           | Metronidazole | 1212030-01       | 2       |
| Caelo                      | Metronidazole | 12339521         | 1       |
| Caelo                      | Metronidazole | 1212030-21       | 1       |
| Fagron                     | Metronidazole | 12f15-n04        | 1       |
| Fagron                     | Metronidazole | 12A20-B07-303298 | 1       |
| Fagron                     | Metronidazole | 12G04-N15        | 19      |
| Fagron                     | Metronidazole | 12L17-N16        | 3       |
| Fagron                     | Metronidazole | 12L17-N11        | 15      |
| Fagron                     | Metronidazole | 13/21-N07        | 2       |
| Caelo                      | Metronidazole | 13041503         | 1       |
| Euro OTC                   | Metronidazole | 1307002-01       | 6       |
| Caelo                      | Metronidazole | 1307002          | 1       |
| Euro OTC                   | Metronidazole | 13070002-02      | 1       |
| GEHE 11.06.2014            | Metronidazole | 1307002-01       | 1       |
| Gehe                       | Metronidazole | 1307002-01       | 1       |
| EuRho/Phönix               | Metronidazole | 1307002-01       | 1       |
| Kuerzel                    | Metronidazole | 1307002-02       | 1       |
| Gehe                       | Metronidazole | 1307002-02       | 1       |
| Euro OTC                   | Metronidazole | 1307002-02       | 1       |
| Fagron                     | Metronidazole | 1307042          | 1       |
| Alliance Health 20.05.2... | Metronidazole | 1307042-01       | 2       |
| Euro OTC                   | Metronidazole | 1307042-02       | 7       |
| Sanacorp                   | Metronidazole | 13095002         | 1       |
| Caelo                      | Metronidazole | 13095002         | 8       |
| Caelo                      | Metronidazole | 13095003         | 16      |
| Fagron                     | Metronidazole | 13095002         | 1       |
| Cealo/Sanacorp             | Metronidazole | 13095003         | 1       |
| Caelo                      | Metronidazole | 13095004         | 12      |
| Caelo                      | Metronidazole | 13095005         | 7       |
| Ichthyol Gesellschaft      | Metronidazole | 13095005         | 1       |
| Caelo                      | Metronidazole | 13095006         | 7       |
| Anzag 21.10.14 EK 2.85     | Metronidazole | 13095007         | 1       |
| Caelo                      | Metronidazole | 13095007         | 7       |
| Caelo                      | Metronidazole | 13095011         | 3       |

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| Supplier                   | Substance     | Batch      | Spectra |
|----------------------------|---------------|------------|---------|
| Caelo                      | Metronidazole | 13095012   | 12      |
| Noweda                     | Metronidazole | 13095012   | 1       |
| AHD 22.09.14 EK 4,52       | Metronidazole | 13095013   | 1       |
| Caelo                      | Metronidazole | 13095013   | 12      |
| Caelo                      | Metronidazole | 13095017   | 6       |
| Caesar & Lorenz            | Metronidazole | 13095013   | 1       |
| Caelo                      | Metronidazole | 13095018   | 6       |
| Caelo                      | Metronidazole | 13095019   | 7       |
| Caelo                      | Metronidazole | 13095020   | 7       |
| Caelo                      | Metronidazole | 13214001   | 15      |
| VDL 07.11.14               | Metronidazole | 13214001   | 1       |
| Caelo                      | Metronidazole | 13214002   | 19      |
| Caelo                      | Metronidazole | 13214003   | 12      |
| Caelo                      | Metronidazole | 132140022  | 1       |
| Caelo                      | Metronidazole | 13214009   | 6       |
| Sanacorp 02.03.15          | Metronidazole | 13214009   | 1       |
| Caelo                      | Metronidazole | 13214010   | 5       |
| Caelo                      | Metronidazole | 13214012   | 5       |
| Caelo                      | Metronidazole | 13214011   | 1       |
| Caesar & Loretz GmbH Hi... | Metronidazole | 13214013   | 1       |
| Caelo                      | Metronidazole | 13214013   | 1       |
| Caelo                      | Metronidazole | 13214014   | 6       |
| Caelo                      | Metronidazole | 13214015   | 6       |
| Caelo                      | Metronidazole | 13214016   | 2       |
| Caelo                      | Metronidazole | 13214017   | 2       |
| Phönix                     | Metronidazole | 13214017   | 1       |
| Phönix Gotha               | Metronidazole | 13214017   | 1       |
| Noweda/Wepa                | Metronidazole | 13214017   | 1       |
| Caelo                      | Metronidazole | 13214018   | 5       |
| Caelo                      | Metronidazole | 13214019   | 7       |
| Caelo                      | Metronidazole | 13214021   | 1       |
| Caelo                      | Metronidazole | 13214024   | 3       |
| Caelo                      | Metronidazole | 13214025   | 4       |
| Noweda                     | Metronidazole | 13214025   | 1       |
| Caelo                      | Metronidazole | 13214029   | 6       |
| Anzag/Henry Lamotte        | Metronidazole | 13214029   | 1       |
| Caelo                      | Metronidazole | 1321409    | 1       |
| Fagron                     | Metronidazole | 13D10-N02  | 3       |
| Fagron                     | Metronidazole | 13I10-N03  | 3       |
| Fagron                     | Metronidazole | 13J21-N07  | 36      |
| Fagron                     | Metronidazole | 13J21N07   | 3       |
| Fagron                     | Metronidazole | 13j21-n07  | 3       |
| Caelo                      | Metronidazole | 13J21-N07  | 1       |
| Fagron                     | Metronidazole | 13j21-N07  | 1       |
| EuRho                      | Metronidazole | 1406010-01 | 1       |
| Euro OTC                   | Metronidazole | 1406010-01 | 18      |
| Euro OTC                   | Metronidazole | 140601001  | 2       |
| Pphoenix goettin           | Metronidazole | 1406010-01 | 1       |
| Eurho                      | Metronidazole | 1406010-01 | 1       |
| Eurimpharm                 | Metronidazole | 140601001  | 1       |
| Euro OTC                   | Metronidazole | 1407003    | 1       |
| Euro OTC                   | Metronidazole | 1407003-01 | 8       |
| Euro OTC                   | Metronidazole |            | 1       |
| Euro OTC                   | Metronidazole | 140700301  | 1       |
| Euro OTC                   | Metronidazole | 140700302  | 2       |
| Euro OTC                   | Metronidazole | 1407003-02 | 4       |
| Euro OTC                   | Metronidazole | 1412016-01 | 12      |
| Caelo                      | Metronidazole | 1412016-01 | 4       |
| Euro OTC                   | Metronidazole | 1412016-02 | 21      |
| Euro OTC                   | Metronidazole | 141201601  | 1       |

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| <b>Supplier</b>        | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|------------------------|------------------|-------------------|----------------|
| Caelo                  | Metronidazole    | 1412016-02        | 1              |
| Fagron                 | Metronidazole    | 1414-B02-291237   | 1              |
| Fagron                 | Metronidazole    | 141C14-B02-296437 | 1              |
| Farchemia Srl/Sanacorp | Metronidazole    | 146010-01         | 1              |
| Fagron                 | Metronidazole    | 14B27-B31-291230  | 1              |
| Fagron                 | Metronidazole    | 14B27-B31-291234  | 1              |
| Fagron                 | Metronidazole    | 14B27-B31-291235  | 1              |
| Fagron                 | Metronidazole    | 14C14-802-291237  | 1              |
| Fagron                 | Metronidazole    | 14B-B02-291275    | 1              |
| Fagron                 | Metronidazole    | 14C14B02-291276   | 2              |
| Fagron                 | Metronidazole    | 14C14-B01-306363  | 3              |
| Fagron                 | Metronidazole    | 14C14-B01         | 1              |
| Fagron                 | Metronidazole    | 14C14B02          | 3              |
| Fagron                 | Metronidazole    | 14C14-B01-309058  | 2              |
| Fagron                 | Metronidazole    | 14C14-B02         | 5              |
| Fagron                 | Metronidazole    | 14c14-b02-21238   | 1              |
| Fagron                 | Metronidazole    | 14C14-B02-291237  | 8              |
| Fagron                 | Metronidazole    | 14C14-B02-291239  | 1              |
| Caelo                  | Metronidazole    | 14C14-B02-291237  | 2              |
| Fagron                 | Metronidazole    | 14C14-B02-291238  | 2              |
| Fagron                 | Metronidazole    | 14C14-B02-291239  | 7              |
| Fargon                 | Metronidazole    | 14c14-b02-291238  | 1              |
| Fagron                 | Metronidazole    | 14c14-b02-291239  | 1              |
| Caelo                  | Metronidazole    | 14C14-B02-291239  | 1              |
| Fagron                 | Metronidazole    | 14C14-B02-291241  | 1              |
| Fagron                 | Metronidazole    | 14C14-B02-291275  | 6              |
| Fagron                 | Metronidazole    | 14c14-b02-291275  | 1              |
| Fagron                 | Metronidazole    | 14C14-B02-291276  | 3              |
| Fagron                 | Metronidazole    | 14c14b02291276    | 1              |
| Fagron                 | Metronidazole    | 14c14-b02-291276  | 2              |
| Fagron                 | Metronidazole    | 14C14-B02-295603  | 1              |
| Caelo                  | Metronidazole    | 14C14-B02-291276  | 1              |
| Fagron                 | Metronidazole    | 14C14-B02-296437  | 6              |
| Fagron                 | Metronidazole    | 14-C14-B02-296437 | 1              |
| Fagron                 | Metronidazole    | 14C14-B02-300182  | 3              |
| Gehe01/2018            | Metronidazole    | 14C14-B02-291237  | 1              |
| Fagron                 | Metronidazole    | 14C14-B291237     | 1              |
| Fagron                 | Metronidazole    | 14C14-Bo2-291276  | 1              |
| Euro OTC               | Metronidazole    | 1503004-01        | 1              |
| Fagron                 | Metronidazole    |                   | 1              |
| Euro OTC               | Metronidazole    | 1505024           | 1              |
| Euro OTC               | Metronidazole    | 1505024-01        | 8              |
| Euro OTC               | Metronidazole    | 150502401         | 1              |
| Euro OTC               | Metronidazole    | 1505024-02        | 4              |
| Euro OTC               | Metronidazole    | 1508004-01        | 15             |
| Caelo                  | Metronidazole    | 1508004-01        | 1              |
| Euro OTC               | Metronidazole    | 1508004-02        | 8              |
| Euro/ Sanacorp         | Metronidazole    | 150800402         | 1              |
| Euro OTC               | Metronidazole    | 150804-01         | 1              |
| Caelo                  | Metronidazole    | 15215103          | 4              |
| Caelo                  | Metronidazole    | 15215104          | 6              |
| Caelo                  | Metronidazole    | 1521503           | 1              |
| Caelo                  | Metronidazole    | 15215105          | 2              |
| Caelo                  | Metronidazole    | 15215106          | 4              |
| Caelo                  | Metronidazole    | 15215108          | 7              |
| Caelo                  | Metronidazole    | 15215107          | 1              |
| Caelo                  | Metronidazole    | 15253001          | 9              |
| Caelo                  | Metronidazole    | 1523013           | 1              |
| Caelo                  | Metronidazole    | 1523026           | 1              |
| Caelo                  | Metronidazole    | 15253003          | 8              |

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| Supplier                     | Substance     | Batch              | Spectra |
|------------------------------|---------------|--------------------|---------|
| Caelo                        | Metronidazole | 15253002           | 1       |
| Caesar&Loretz GmbH/Sana...   | Metronidazole | 15253003           | 1       |
| Caelo                        | Metronidazole | 15253004           | 8       |
| Caelo                        | Metronidazole | 15253005           | 2       |
| Caelo                        | Metronidazole | 15253006           | 6       |
| Caelo                        | Metronidazole | 15253007           | 7       |
|                              | Metronidazole | 15253007           | 2       |
| Caelo                        | Metronidazole | 15253011           | 8       |
| Caelo                        | Metronidazole | 15253013           | 5       |
| Caelo                        | Metronidazole | 15253015           | 8       |
| Caelo                        | Metronidazole | 15253016           | 7       |
| Caesar & Loretz GmbH Hi...   | Metronidazole | 15253016           | 1       |
| Caelo                        | Metronidazole | 15253017           | 8       |
| Caesar & Loretz GmbH         | Metronidazole | 15253017           | 1       |
| Phönix                       | Metronidazole | 15253018           | 1       |
| Caelo                        | Metronidazole | 15253018           | 4       |
| Caelo                        | Metronidazole | 15253019           | 2       |
| Caelo                        | Metronidazole | 15253020           | 5       |
| Caelo                        | Metronidazole | 15253021           | 5       |
| Caelo                        | Metronidazole | 15253024           | 3       |
| Caelo                        | Metronidazole | 15253022           | 1       |
| Caelo                        | Metronidazole | 15253026           | 9       |
| Caelo                        | Metronidazole | 15253027           | 9       |
| Euro OTC                     | Metronidazole | 15253027           | 1       |
| Phoenix 12.10.2016 6,63EUR   | Metronidazole | 15253027           | 1       |
| Caelo                        | Metronidazole | 15253028           | 3       |
| Caelo                        | Metronidazole | 15253029           | 1       |
| Bombastus                    | Metronidazole | 15253032           | 1       |
| Farchemia S.R.L./ Caesa...   | Metronidazole | 15253032           | 1       |
| sanacorp, 9,51EUR, 14.09.... | Metronidazole | 15253029           | 1       |
| Caelo                        | Metronidazole | 15253032           | 2       |
| Caelo                        | Metronidazole | 15253033           | 3       |
| Fagron                       | Metronidazole | 15A20-B07          | 1       |
| Fagron                       | Metronidazole | 15A20-B07-303293   | 6       |
| Fagron                       | Metronidazole | 15A20-B07-303294   | 2       |
| Euro OTC                     | Metronidazole | 15a20-b07-303294   | 1       |
| Fagron                       | Metronidazole | 15A20-B07-303294Mg | 1       |
| Fagron                       | Metronidazole | 15A20-B07-303295   | 2       |
| Fagron                       | Metronidazole | 15A20-B07-303298   | 5       |
| Caelo                        | Metronidazole | 15A20-B07-303297   | 1       |
| Fagron                       | Metronidazole | 15a20-b07-308196   | 1       |
| Fagron                       | Metronidazole | 15A20-B07-308196   | 3       |
| Caelo                        | Metronidazole | 15A20-B07-303298   | 1       |
| Fagron                       | Metronidazole | 15A20-B07-308525   | 4       |
| Fischer/Gehe                 | Metronidazole | 15A20-B07-308525   | 1       |
| Fagron                       | Metronidazole | 15A20B07308525     | 1       |
| Fagron                       | Metronidazole | 15A20-B07-308791   | 3       |
| Fagron                       | Metronidazole | 15a20-b07-308791   | 1       |
| Fagron                       | Metronidazole | 15A20-B07-312057   | 4       |
| Fagron                       | Metronidazole | 15A20-B07312057    | 1       |
| Fagron                       | Metronidazole | 15A20-B07-312225   | 2       |
| Fagron                       | Metronidazole | 15A20-B07-31225    | 1       |
| Fagron                       | Metronidazole | 16/19-B04-326152   | 2       |
| Fagron                       | Metronidazole | 16/19-B04-326155   | 2       |
| Caelo                        | Metronidazole | 16/19-B04-326155   | 1       |
| Fagron                       | Metronidazole | 16/19-B04-329168   | 2       |
| Fagron                       | Metronidazole | 16/19-b04-329168   | 1       |
| Phoenix                      | Metronidazole | 16089201           | 1       |
| Caelo                        | Metronidazole | 16089202           | 6       |
| Caelo                        | Metronidazole | 16089201           | 1       |

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| Supplier                   | Substance     | Batch             | Spectra |
|----------------------------|---------------|-------------------|---------|
| Fagron                     | Metronidazole | 16/19bo4326155    | 1       |
| Caelo                      | Metronidazole | 16089209          | 4       |
| Caelo                      | Metronidazole | 16089212          | 8       |
| AHD 03.02.17               | Metronidazole | 16089212          | 1       |
| Caelo                      | Metronidazole | 16089213          | 5       |
| Caelo                      | Metronidazole | 16089215          | 5       |
| Caelo                      | Metronidazole | 16089216          | 2       |
| hochhaus-Apotheke          | Metronidazole | 16089215          | 1       |
| Caelo                      | Metronidazole | 16089218          | 4       |
| Caelo                      | Metronidazole | 16089219          | 3       |
| Caelo                      | Metronidazole | 16089220          | 4       |
| Caelo                      | Metronidazole | 16089221          | 2       |
| Caelo                      | Metronidazole | 16089222          | 1       |
| Apotheke an der Bornhei... | Metronidazole | 16089223          | 1       |
| Caelo                      | Metronidazole | 16089224          | 1       |
| Ebert-Jacobi               | Metronidazole | 16089224          | 1       |
| Fagron                     | Metronidazole | 16089235          | 1       |
| Euro/Sanacorp              | Metronidazole | 1609028           | 1       |
| Euro OTC                   | Metronidazole | 1609028-01        | 8       |
| Caelo                      | Metronidazole | 160902801         | 1       |
| EURO / Sanacorp            | Metronidazole | 160902801         | 1       |
| Caelo                      | Metronidazole | 1609028-01        | 2       |
| Farchemia/Phönix           | Metronidazole | 1609028-02        | 1       |
| Euro OTC                   | Metronidazole | 1612013-01        | 1       |
| Fagron                     | Metronidazole | 1619b04326155     | 1       |
| Fagron                     | Metronidazole | 16I19-B04         | 3       |
| Fagron                     | Metronidazole | 16I19-B04-326150  | 1       |
| Fagron                     | Metronidazole | 16I19-B04-326151  | 2       |
| Fagron                     | Metronidazole | 16I19-B04-326155  | 3       |
| EuRho                      | Metronidazole | 1701039-01        | 1       |
| Fagron                     | Metronidazole | 17/19-304-329168  | 1       |
| Fagron                     | Metronidazole | 16J19-B04-326151  | 1       |
| Euro OTC                   | Metronidazole | 1701039-01        | 4       |
| Fagron                     | Metronidazole | 16I19-B04-329165  | 1       |
| Caelo                      | Metronidazole | 17058002          | 1       |
| Caelo                      | Metronidazole | 18071401          | 1       |
| Fagron                     | Metronidazole | 172939-B01-295547 | 1       |
| Euro OTC                   | Metronidazole | 20120974          | 1       |
| Fagron                     | Metronidazole | 19I19-B04-326154  | 1       |
| Fagron                     | Metronidazole | 20130906F         | 4       |
| Fagron                     | Metronidazole | 20140131F         | 3       |
| Caelo                      | Metronidazole | 23011504          | 1       |
| Sanacorp                   | Metronidazole | 39/AKD18          | 1       |
| Sanacorp                   | Metronidazole | 39/AKD6           | 1       |
| Caelo                      | Metronidazole | 39/AKD4           | 1       |
| Caelo                      | Metronidazole | 27092014A         | 1       |
| Caelo                      | Metronidazole | 39/AKD7           | 1       |
| Caelo                      | Metronidazole | 41/AKD16          | 1       |
| Fagron                     | Metronidazole | 606/10072017      | 1       |
| Caelo                      | Metronidazole |                   | 1       |
| Sanacorp                   | Metronidazole |                   | 2       |
| Caelo                      | Metronidazole | 102311870         | 1       |
| Caelo                      | Metronidazole | P145/14           | 1       |
| Caelo                      | Metronidazole | 614U1870          | 1       |
| Caelo                      | Metronidazole | 8012014B          | 1       |
| Caelo                      | Metronidazole | 2071304           | 1       |
| Caelo                      | Metronidazole | 1210411           | 1       |
| Fagron                     | Metronidazole | 8I10-N19          | 1       |
| Caelo                      | Metronidazole | 607211870         | 1       |
| Euro OTC                   | Metronidazole | 1220150132        | 1       |

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| <b>Supplier</b>       | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|-----------------------|------------------|--------------|----------------|
| Caelo                 | Metronidazole    | 10368313     | 1              |
| Caelo                 | Metronidazole    | 10368311     | 1              |
| Caelo                 | Metronidazole    | 10112907     | 1              |
| Caelo                 | Metronidazole    | 10368318     | 1              |
| Fagron                | Metronidazole    | 9041303      | 1              |
| Gehe                  | Metronidazole    | 10368318     | 1              |
| Caelo                 | Metronidazole    | 9175609      | 1              |
| Euro OTC              | Metronidazole    | 1003028-02   | 1              |
| Caelo                 | Metronidazole    | 10368319     | 1              |
| Caelo                 | Metronidazole    | 10368320     | 1              |
| Euro OTC              | Metronidazole    | 1101017-03   | 1              |
| Fargon                | Metronidazole    | 1101017-01   | 1              |
| Fagron                | Metronidazole    | 10F23-N05    | 1              |
| Phoenix am 11.06.2012 | Metronidazole    | 1101017-03   | 2              |
| Euro OTC              | Metronidazole    | 1101017-3    | 1              |
| Euro OTC              | Metronidazole    | 1109016-01   | 4              |
| ANZAG am 18.05.2012   | Metronidazole    | 1109016-01   | 1              |
| Euro OTC              | Metronidazole    | 1109030-01   | 7              |
| Post-Apotheke         | Metronidazole    | 1109030-01   | 1              |
| Caelo                 | Metronidazole    | 1109030-01   | 2              |
| Euro OTC              | Metronidazole    | 1109030-02   | 2              |
| Post-Apotheke         | Metronidazole    | 1109030-02   | 1              |
| EuRho                 | Metronidazole    | 1109030-02   | 1              |
| EuRho                 | Metronidazole    | 110903002    | 1              |
| Euro OTC              | Metronidazole    | 1109030-03   | 3              |
| Anzag 09.07.2013      | Metronidazole    | 1112028      | 1              |
| Phönix                | Metronidazole    | 1109030-03   | 1              |
| Euro OTC              | Metronidazole    | 1112028-01   | 6              |
| Euro OTC              | Metronidazole    | 1112028-02   | 7              |
| Caelo                 | Metronidazole    | 1112028-02   | 2              |
| Gehe                  | Metronidazole    | 1112028-02   | 1              |
| Gehe 08.06.2013       | Metronidazole    | 111202802    | 1              |
| Anzag 09.07.2013      | Metronidazole    | 1112028-02   | 1              |
| Fagron                | Metronidazole    | 112356       | 1              |
| Caelo                 | Metronidazole    | 11319806     | 1              |
| Caelo                 | Metronidazole    | 11319807     | 1              |
| Caelo                 | Metronidazole    | 11319809     | 1              |
| Caelo                 | Metronidazole    | 11319812     | 1              |
| Caelo                 | Metronidazole    | 11319816     | 2              |
| Caelo                 | Metronidazole    | 11319817     | 1              |
| Kehr                  | Metronidazole    | 11319817     | 1              |
| VDL                   | Metronidazole    | 11319816     | 1              |
| Caelo                 | Metronidazole    | 11319818     | 4              |
| Spangropharm          | Metronidazole    | 11319818     | 1              |
| Noweda                | Metronidazole    | 11319818     | 2              |
| Caelo                 | Metronidazole    | 11319819     | 1              |
| Caelo                 | Metronidazole    | 11319823     | 6              |
| Caelo                 | Metronidazole    | 11319824     | 3              |
| Noweda                | Metronidazole    | 11319824     | 1              |
| Caelo                 | Metronidazole    | 11319825     | 6              |
| Kehr                  | Metronidazole    | 11319825     | 1              |
| Anzag                 | Metronidazole    | 11373512     | 1              |
| Fagron                | Metronidazole    | 11C21-N01    | 2              |
| Fagron                | Metronidazole    | 11F15-N07    | 1              |
| Fagron                | Metronidazole    | 11F15-N07    | 1              |
| Fagron                | Metronidazole    | 11H11-n03    | 1              |
| Caelo                 | Metronidazole    | 11h11-n03    | 1              |
| Fagron                | Metronidazole    | 11J07-N07    | 1              |
| Noweda                | Metronidazole    | 11J07-N07    | 1              |
| Caelo                 | Metronidazole    | 12110121     | 1              |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|----------------------------|------------------|--------------|----------------|
| Caelo                      | Metronidazole    | 12110105     | 1              |
| Noweda                     | Metronidazole    | 12110404     | 1              |
| Caelo                      | Metronidazole    | 1201156      | 1              |
| Caelo                      | Metronidazole    | 12110403     | 1              |
| Caelo                      | Metronidazole    | 12110405     | 9              |
| Kehr                       | Metronidazole    | 1210411      | 1              |
| Noweda                     | Metronidazole    | 12110405     | 1              |
| Caesar&Loretz,Phoenix      | Metronidazole    | 12110410     | 1              |
| Caelo                      | Metronidazole    | 12110411     | 8              |
| Caelo                      | Metronidazole    | 12110410     | 2              |
| Gehe                       | Metronidazole    | 12110410     | 1              |
| Caelo                      | Metronidazole    | 121104085    | 1              |
| Caelo                      | Metronidazole    | 12110412     | 8              |
| Fargon                     | Metronidazole    | 12110412     | 1              |
| Caelo                      | Metronidazole    | 12110413     | 6              |
| Phönix Gotha               | Metronidazole    | 12110413     | 1              |
| Caelo                      | Metronidazole    | 12110414     | 3              |
| Noweda                     | Metronidazole    | 12110415     | 1              |
| Caelo                      | Metronidazole    | 12110415     | 4              |
| Gehe                       | Metronidazole    | 12110415     | 1              |
| Alliance Healthcare        | Metronidazole    | 12110415     | 1              |
| Caelo                      | Metronidazole    | 12110421     | 9              |
| vdl                        | Metronidazole    | 12110421     | 1              |
| Sanacorp                   | Metronidazole    | 12110422     | 1              |
| Caelo                      | Metronidazole    | 12110422     | 19             |
| Gehe                       | Metronidazole    | 12110422     | 1              |
| Caelo                      | Metronidazole    | 12110423     | 2              |
| Caelo                      | Metronidazole    | 1211413      | 1              |
| Caelo                      | Metronidazole    | 121145       | 1              |
| Euro OTC                   | Metronidazole    | 1212001-01   | 11             |
| Henry Lamotte              | Metronidazole    | 1212001-02   | 1              |
| Phönix 08.11.2013          | Metronidazole    | 1212001-02   | 1              |
| Alliance Health 23.01.2... | Metronidazole    | 1212001-02   | 1              |
| Euro OTC                   | Metronidazole    | 1212030-01   | 5              |
| geh 30.08.13               | Metronidazole    | 121203001    | 1              |
| Phönix                     | Metronidazole    | 121203001    | 1              |
| Caelo                      | Metronidazole    | 12339501     | 7              |
| Phoenix                    | Metronidazole    | 121203002    | 1              |
| Caelo                      | Metronidazole    | 12339        | 1              |
| Noweda                     | Metronidazole    | 12339501     | 1              |
| Caelo                      | Metronidazole    | 12339502     | 25             |
| gehe 11.06.2013            | Metronidazole    | 12339502     | 1              |
| Alliance                   | Metronidazole    | 12339502     | 1              |
| Caelo                      | Metronidazole    | 12339503     | 5              |
| Caelo                      | Metronidazole    | 12339504     | 10             |
| Caelo                      | Metronidazole    | 12339507     | 9              |
| Caelo                      | Metronidazole    | 12339508     | 5              |
| Caelo                      | Metronidazole    | 12339509     | 4              |
| Phönix, 02.10.13           | Metronidazole    | 12339508     | 1              |
| Caelo                      | Metronidazole    | 12339510     | 14             |
| Gehe                       | Metronidazole    | 12339509     | 1              |
| Post-Apotheke              | Metronidazole    | 12339510     | 1              |
| Caelo                      | Metronidazole    | 12339511     | 15             |
| Phönix/Maros               | Metronidazole    | 12339511     | 1              |
| Caesar&Loretz GmbH/Anzag   | Metronidazole    | 12339511     | 1              |
| Caelo                      | Metronidazole    | 12339519     | 13             |
| Sanacorp                   | Metronidazole    | 12339519     | 1              |
| Caelo                      | Metronidazole    | 12339520     | 5              |
| Caesar & Loretz GmbH Hi... | Metronidazole    | 12339520     | 1              |
| Caelo                      | Metronidazole    | 1239503      | 1              |

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| Supplier                  | Substance     | Batch            | Spectra |
|---------------------------|---------------|------------------|---------|
| Fagron                    | Metronidazole | 12D30-N02        | 1       |
| Fagron                    | Metronidazole | 12D30-N03        | 4       |
| Caelo                     | Metronidazole | 1239504          | 1       |
| Fagron                    | Metronidazole | 12F15-N04        | 9       |
| Euro OTC                  | Metronidazole | 12F15-N04        | 1       |
| Fagron                    | Metronidazole | 12g04-n15        | 1       |
| Noweda                    | Metronidazole | 12G04-N15        | 1       |
| Sanacorp                  | Metronidazole | 12G04-N15        | 1       |
| A.H. 19.02.13 ek: 5,86EUR | Metronidazole | 12G04-N15        | 1       |
| Fagron                    | Metronidazole | 12L17N16         | 1       |
| Fagron                    | Metronidazole | 12L17N11         | 1       |
| Erika apotheke            | Metronidazole | 12L17-N11        | 2       |
| Caelo                     | Metronidazole | 12L17-N11        | 4       |
| Fagron                    | Metronidazole | 12L17-n11        | 1       |
| Phönix                    | Metronidazole | 12L17-N11        | 1       |
| Sanacorp                  | Metronidazole | 12L17-N16        | 1       |
| Fagron                    | Metronidazole | 12L-N11          | 1       |
| Euro OTC                  | Metronidazole | 130704201        | 1       |
| Caelo                     | Metronidazole | 13095001         | 11      |
| Euro OTC                  | Metronidazole | 1308704201       | 1       |
| gehe                      | Metronidazole | 13095005         | 1       |
| Caelo                     | Metronidazole | 13B06-N023       | 1       |
| Fagron                    | Metronidazole | 13B06-N03        | 16      |
| Fagron                    | Metronidazole | 13B06N03         | 1       |
| Euro OTC                  | Metronidazole | 13B06-N03        | 1       |
| Fagron                    | Metronidazole | 13D08N22         | 1       |
| Fargon                    | Metronidazole | 13D08-N22        | 1       |
| Fargon                    | Metronidazole | 13D08-n22        | 1       |
| Fagron                    | Metronidazole | 13D08-N22        | 8       |
| Phönix                    | Metronidazole | 13J21-N07        | 1       |
| Fagron                    | Metronidazole | 140700301        | 1       |
| Caelo                     | Metronidazole | 14111304         | 1       |
| Euro OTC                  | Metronidazole | 14120601         | 1       |
| Caelo                     | Metronidazole | 14B27-B31-291230 | 1       |
| Fagron                    | Metronidazole | 14C14-B02291238  | 1       |
| Euro OTC                  | Metronidazole | 150502403        | 1       |
| Caelo                     | Metronidazole | 15121202         | 1       |
| Phönix                    | Metronidazole | 15253002         | 1       |
| Euro OTC                  | Metronidazole | 20111025         | 1       |
| Caelo                     | Metronidazole | 18051201         | 1       |
| Caelo                     | Metronidazole | 201007126        | 1       |
| Fagron                    | Metronidazole | 20121121         | 3       |
| Caelo                     | Metronidazole | 2013U-01870      | 2       |
| Caelo                     | Metronidazole | 20140612-12      | 1       |
| Caelo                     | Metronidazole | 2813E1870        | 1       |
| Caelo                     | Metronidazole | 28061204         | 1       |
| Caelo                     | Metronidazole | 30131-01870      | 1       |
| Caelo                     | Metronidazole | 3112M-01870      | 1       |
| Fagron                    | Metronidazole | 3212E01870       | 1       |
| Phoenix                   | Metronidazole |                  | 1       |
| Caelo                     | Metronidazole | 39/AKD16         | 1       |
| Caelo                     | Metronidazole | MTZ/2050401      | 1       |
| Euro OTC                  | Metronidazole | 700837           | 1       |
| Henry Lamotte             | Metronidazole | 5448100          | 1       |
| Sanacorp                  | Metronidazole | 39AKD15          | 1       |
| Fagron                    | Metronidazole | Ch12L17-N11      | 1       |
| Caelo                     | Metronidazole | 10368310         | 1       |
| Euro OTC                  | Metronidazole | F120017          | 1       |
| Caelo                     | Metronidazole | 11319810         | 2       |
| Euro OTC                  | Metronidazole | 110903002        | 1       |

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| Supplier | Substance     | Batch      | Spectra |
|----------|---------------|------------|---------|
| Caelo    | Metronidazole | 1112028-01 | 1       |
| Caelo    | Metronidazole | 12339527   | 1       |
| Fagron   | Metronidazole | 12a2o-n18  | 1       |

- 68 246 spectra from 414 *Apo-Ident* customers from a total of 23 448 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Metronidazole* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Metronidazole* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 370           | 0              | 146 359       |
| <b>Type C</b> | 0              | 1318          | 69             | 68 246        |

The substance/substance group *Metronidazole* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.3784 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 95.0252 % (> 94.8089 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20857     | 22472               | 14.38                        | 66.60                           |

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| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21212            | 22472                      | 4.05                                | 68.45                                  |
| 21213            | 22472                      | 5.30                                | 69.06                                  |
| 21356            | 21881                      | 11.22                               | 67.85                                  |
| 21881            | 21881                      | 0.00                                | 69.44                                  |
| 22472            | 22472                      | 0.00                                | 68.48                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Miconazole nitrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20210-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Miconazole nitrate; Miconazoli nitras; Miconazolum nitricum

### Special notes

When selecting the *Miconazole nitrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Miconazole nitrate*:

| Supplier | Substance          | Batch      | Sample ID | Spectra | Certificate |
|----------|--------------------|------------|-----------|---------|-------------|
| Fagron   | Miconazole nitrate | 13D22-N14  | 20817     | 85      | 20130529    |
| Caelo    | Miconazole nitrate | 13185601   | 20875     | 40      | 20130704    |
| Caelo    | Miconazole nitrate | 13352802   | 21350     | 39      | 1412250     |
| Euro OTC | Miconazole nitrate | 1307025-02 | 21649     | 40      | 20130806    |
| Euro OTC | Miconazole nitrate | 1509014    | 21900     | 40      | 20150930*   |
| Caelo    | Miconazole nitrate | 161447     | 22630     | 40      | 20160617*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 284 spectra of 6 reference samples from the substance/substance group *Miconazole nitrate*. These samples are listed above in the [calibration samples](#) section.
- 71 102 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 698 spectra of 18 reference samples from the substance/substance group *Miconazole nitrate*.

| Supplier | Substance          | Batch      | Sample ID          | Spectra |
|----------|--------------------|------------|--------------------|---------|
| Caelo    | Miconazole nitrate | 10122908   | 20210              | 40      |
| Fagron   | Miconazole nitrate | 13D22-N14  | 20817 <sup>†</sup> | 5       |
| Caelo    | Miconazole nitrate | 13185601   | 20905              | 80      |
| Caelo    | Miconazole nitrate | 13352802   | 21351              | 40      |
| Euro OTC | Miconazole nitrate | 1307025-02 | 21649 <sup>†</sup> | 20      |
| Euro OTC | Miconazole nitrate | 1509014    | 21900 <sup>†</sup> | 20      |
| Euro OTC | Miconazole nitrate | 1604004    | 22522              | 40      |
| Euro OTC | Miconazole nitrate | 1607004    | 22671              | 40      |
| Euro OTC | Miconazole nitrate | 1611024    | 22920              | 40      |
| Euro OTC | Miconazole nitrate | 1705039    | 23429              | 40      |
| Caelo    | Miconazole nitrate | 172175     | 23662              | 40      |
| Caelo    | Miconazole nitrate | 13185601   | 20875SI            | 60      |
| Euro OTC | Miconazole nitrate | 1307025-02 | 21649SI            | 37      |
| Euro OTC | Miconazole nitrate | 1509014    | 21900SI            | 53      |
| Euro OTC | Miconazole nitrate | 1604004    | 22522SI            | 36      |
| Caelo    | Miconazole nitrate | 161447     | 22630SI            | 40      |
| Euro OTC | Miconazole nitrate | 1607004    | 22671SI            | 30      |
| Euro OTC | Miconazole nitrate | 1611024    | 22920SI            | 37      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 031 spectra from a total of 3182 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 761 spectra from 194 *Apo-Ident* customers from 201 batches from the substance/substance group *Miconazole nitrate*.

| Supplier                 | Substance          | Batch            | Spectra |
|--------------------------|--------------------|------------------|---------|
| Caelo                    | Miconazole nitrate | 12374307         | 18      |
| Euro OTC                 | Miconazole nitrate | 1504003-01       | 1       |
| Caelo                    | Miconazole nitrate | 15137902         | 12      |
| Caelo                    | Miconazole nitrate | 15137903         | 12      |
| Fagron                   | Miconazole nitrate | 15137905         | 1       |
| Caelo                    | Miconazole nitrate | 15137913         | 3       |
| Fagron                   | Miconazole nitrate | 15i08-b07-312317 | 1       |
| Fagron                   | Miconazole nitrate | 15a13-b07-308432 | 1       |
| Caelo                    | Miconazole nitrate | 16144711         | 3       |
| Fagron                   | Miconazole nitrate | 15i08-b07-315481 | 1       |
| Caelo                    | Miconazole nitrate | 16144704         | 4       |
| Caelo                    | Miconazole nitrate | 12243803         | 11      |
| Anzag                    | Miconazole nitrate | 12243801         | 1       |
| Anzag                    | Miconazole nitrate | 12H10-N02        | 1       |
| Fagron                   | Miconazole nitrate | 12h10-n02        | 1       |
| Fagron                   | Miconazole nitrate | 12K02-N06        | 7       |
| Fagron                   | Miconazole nitrate | 13H28-N06        | 19      |
| Caelo                    | Miconazole nitrate | 10/AKD11         | 1       |
| Gehe                     | Miconazole nitrate | 14149301         | 1       |
| Caelo                    | Miconazole nitrate | 1122014A         | 1       |
| Caelo                    | Miconazole nitrate | 11104109         | 2       |
| Fagron                   | Miconazole nitrate | 13061501         | 1       |
| Caelo                    | Miconazole nitrate | 13185609         | 7       |
| Großhandel               | Miconazole nitrate | 13185610         | 2       |
| Caelo                    | Miconazole nitrate | 13185610         | 8       |
| Phoenix                  | Miconazole nitrate | 13185611         | 1       |
| Caelo                    | Miconazole nitrate | 13185612         | 5       |
| Caelo                    | Miconazole nitrate | 13342801         | 1       |
| Caelo                    | Miconazole nitrate | 13352801         | 19      |
| Caelo                    | Miconazole nitrate |                  | 3       |
| Herbasinica              | Miconazole nitrate | 13352801         | 1       |
| Gehe am 29.04.2014       | Miconazole nitrate | 13352802         | 4       |
| Caelo                    | Miconazole nitrate | 13352802         | 14      |
| Caesar&Loretz GmbH/Anzag | Miconazole nitrate | 13352802         | 1       |
| Caelo                    | Miconazole nitrate | 13352805         | 1       |
| Caelo                    | Miconazole nitrate | 13352806         | 8       |
| Bombastus                | Miconazole nitrate | 13352806         | 1       |
| Fagron                   | Miconazole nitrate | 13352811         | 2       |
| Caelo                    | Miconazole nitrate | 13352811         | 3       |
| Gehe                     | Miconazole nitrate | 13352811         | 1       |
| Fagron                   | Miconazole nitrate | 13A14-B09-287486 | 5       |
| Fagron                   | Miconazole nitrate | 13A14-B09-287487 | 3       |
| Fagron                   | Miconazole nitrate | 13A14-B09-287488 | 2       |
| Fagron                   | Miconazole nitrate | 14051403         | 1       |
| Euro OTC                 | Miconazole nitrate | 140902301        | 1       |

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| <b>Supplier</b>            | <b>Substance</b>   | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|--------------------|------------------|----------------|
| Euro OTC                   | Miconazole nitrate | 1409023-02       | 2              |
| Euro OTC                   | Miconazole nitrate | 1409023-01       | 1              |
| Euro OTC                   | Miconazole nitrate | 140902302        | 1              |
| Caelo                      | Miconazole nitrate | 14149301         | 14             |
| Phoenix 21.10.14           | Miconazole nitrate | 14149301         | 1              |
| Caesar & Loretz GmbH Hi... | Miconazole nitrate | 14149301         | 1              |
| Caelo                      | Miconazole nitrate | 14149302         | 15             |
| Caelo                      | Miconazole nitrate | 14149303         | 7              |
| Caelo                      | Miconazole nitrate | 14149305         | 1              |
| Gehe 6.03.15               | Miconazole nitrate | 14149308         | 2              |
| Caelo                      | Miconazole nitrate | 14149308         | 7              |
| Caelo                      | Miconazole nitrate | 14149309         | 6              |
| Caelo                      | Miconazole nitrate | 14149310         | 8              |
| Caesar&Loretz GmbH /Anzag  | Miconazole nitrate | 14149310         | 1              |
| GEHE 13.05                 | Miconazole nitrate | 14149311         | 1              |
| Caelo                      | Miconazole nitrate | 14149311         | 13             |
| Noweda                     | Miconazole nitrate | 14149311         | 1              |
| EuroPTC/Phönix             | Miconazole nitrate | 14149316         | 1              |
| Fagron                     | Miconazole nitrate | 14149313         | 1              |
| Caelo                      | Miconazole nitrate | 14149317         | 4              |
| Caelo                      | Miconazole nitrate | 14149318         | 17             |
| Caelo                      | Miconazole nitrate | 1419301          | 1              |
| Fagron                     | Miconazole nitrate | 14B18B02         | 1              |
| Caelo                      | Miconazole nitrate | 1419310          | 1              |
| Fagron                     | Miconazole nitrate | 14B18-B02        | 5              |
| Fagron                     | Miconazole nitrate | 14B18-B02-291249 | 1              |
| Fagron                     | Miconazole nitrate | 14B18-B02-291232 | 4              |
| Caelo                      | Miconazole nitrate | 14B18-B02-291233 | 1              |
| Fagron                     | Miconazole nitrate | 14B18-B02-291233 | 3              |
| Fagron                     | Miconazole nitrate | 14B18B02291233   | 1              |
| Fagron                     | Miconazole nitrate | 14B18-B02-291248 | 6              |
| Fagron                     | Miconazole nitrate | 14D25-B06        | 4              |
| Fagron                     | Miconazole nitrate | 14D25-B06-294958 | 11             |
| Fagron                     | Miconazole nitrate | 14D25B06294958   | 1              |
| Fagron                     | Miconazole nitrate | 14D25-B06-294959 | 7              |
| Fagron                     | Miconazole nitrate | 14D25-B06-294960 | 3              |
| Fagron                     | Miconazole nitrate | 14d25-b06-294960 | 1              |
| Caelo                      | Miconazole nitrate | 14D25-B06-294960 | 3              |
| Fagron                     | Miconazole nitrate | 14D25-B06-299790 | 3              |
| Fagron                     | Miconazole nitrate | 14d25-b06-299790 | 1              |
| Fagron                     | Miconazole nitrate | 14H06-B01-299799 | 5              |
| Fagron                     | Miconazole nitrate | 14H06-B01-299813 | 4              |
| Caelo                      | Miconazole nitrate | 15/05-B07-312317 | 1              |
| Fagron                     | Miconazole nitrate | 15/08-B07-312317 | 1              |
| Fagron                     | Miconazole nitrate | 15/08-B07-315481 | 2              |
| Caelo                      | Miconazole nitrate | 15/08-B07-315481 | 1              |
| Fagron                     | Miconazole nitrate | 15/08-B07-318485 | 1              |
| Fagron                     | Miconazole nitrate |                  | 1              |
| Fagron                     | Miconazole nitrate | 15/08-B07-318686 | 1              |
| EuRho                      | Miconazole nitrate | 1504003-01       | 1              |
| Euro OTC                   | Miconazole nitrate | 1504903-01       | 1              |
| Euro OTC                   | Miconazole nitrate | 1509014-01       | 4              |
| Fagron                     | Miconazole nitrate | 1508-B07-318686  | 1              |
| Noweda                     | Miconazole nitrate | 15137903         | 1              |
| Caelo                      | Miconazole nitrate | 15137905         | 7              |
| Caelo                      | Miconazole nitrate | 15137906         | 1              |
| Caelo                      | Miconazole nitrate | 15137907         | 4              |
| Caelo                      | Miconazole nitrate | 15137908         | 3              |
| Caelo                      | Miconazole nitrate | 15137909         | 1              |
| Caelo                      | Miconazole nitrate | 15137910         | 3              |

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| <b>Supplier</b>     | <b>Substance</b>   | <b>Batch</b>      | <b>Spectra</b> |
|---------------------|--------------------|-------------------|----------------|
| Caesar & Loretz/AHC | Miconazole nitrate | 15137910          | 1              |
| Caelo               | Miconazole nitrate | 15137911          | 1              |
| Caelo               | Miconazole nitrate | 15137915          | 3              |
| Phoenix             | Miconazole nitrate | 15137915          | 1              |
| E+J, 27.09.2016     | Miconazole nitrate | 15137915          | 1              |
| Caelo               | Miconazole nitrate | 15A13-B07         | 1              |
| Fagron              | Miconazole nitrate | 15A13-B07         | 4              |
| Fagron              | Miconazole nitrate | 15A13-B07-306565  | 1              |
| Fagron              | Miconazole nitrate | 15A13-B07-306791  | 4              |
| Fagron              | Miconazole nitrate | 15A13-B07-307140  | 8              |
| Caelo               | Miconazole nitrate | 15A13-B07-308432  | 1              |
| Fagron              | Miconazole nitrate | 15A13-B07-308432  | 3              |
| Phoenix             | Miconazole nitrate | 15E04-B03-327367  | 1              |
| Fagron              | Miconazole nitrate | 15I08-B07         | 3              |
| Caelo               | Miconazole nitrate | 15I08-B07-312317  | 4              |
| Fagron              | Miconazole nitrate | 15I08-B07-3121321 | 1              |
| Fagron              | Miconazole nitrate | 15I08-B07-312317  | 2              |
| Fagron              | Miconazole nitrate | 15I08-B07-312321  | 5              |
| Fagron              | Miconazole nitrate | 15I08-B07-31485   | 1              |
| Fagron              | Miconazole nitrate | 15I08-B07-315481  | 3              |
| Caelo               | Miconazole nitrate | 15I08-B07-315481  | 1              |
| Fagron              | Miconazole nitrate | 15I08-B07-315492  | 1              |
| Fagron              | Miconazole nitrate | 15I08-B07-318485  | 1              |
| Fagron              | Miconazole nitrate | 15I08-B07-318686  | 1              |
| Bombastus           | Miconazole nitrate | 15I08-B07-318686  | 1              |
| Bombastus           | Miconazole nitrate | 15I08-B07-318687  | 1              |
| Fagron              | Miconazole nitrate | 15I08-B07-312321  | 1              |
| Caelo               | Miconazole nitrate | 15I08-B07-314838  | 1              |
| Fagron              | Miconazole nitrate | 15I08-B07-315492  | 1              |
| Caelo               | Miconazole nitrate | 15I08-B07-318686  | 1              |
| Ichthyol/Phoenix    | Miconazole nitrate | 16/098/M          | 1              |
| Caelo               | Miconazole nitrate | 16144701          | 10             |
| Euro OTC            | Miconazole nitrate | 1604004-01        | 2              |
| Euro OTC            | Miconazole nitrate | 16144701          | 1              |
| Caelo               | Miconazole nitrate | 16144702          | 12             |
| Gehe                | Miconazole nitrate | 16144702          | 1              |
| Caelo               | Miconazole nitrate | 16144703          | 4              |
| Caelo               | Miconazole nitrate | 16144710          | 7              |
| Caelo               | Miconazole nitrate | 16144716          | 2              |
| Caelo               | Miconazole nitrate | 16144717          | 4              |
| Caelo               | Miconazole nitrate | 16144718          | 1              |
| Caelo               | Miconazole nitrate | 16144720          | 1              |
| Caelo               | Miconazole nitrate | 16144721          | 1              |
| Fagron              | Miconazole nitrate | 16E04-B03         | 1              |
| Caelo               | Miconazole nitrate | 16E04-B03-321367  | 1              |
| Fagron              | Miconazole nitrate | 16E04-B03-321367  | 1              |
| Caelo               | Miconazole nitrate | 16e04-b03-321367  | 1              |
| Fagron              | Miconazole nitrate | 16E04-B03-322     | 1              |
| Fagron              | Miconazole nitrate | 16E04-B03-322124  | 5              |
| Caelo               | Miconazole nitrate | 16E04-B03-322124  | 1              |
| Euro OTC            | Miconazole nitrate | 16E04-B03-322124  | 1              |
| Fagron              | Miconazole nitrate | 16E04-B03-322131  | 1              |
| Phönix              | Miconazole nitrate | 16E04-B03-322131  | 1              |
| Fagron              | Miconazole nitrate | 16E04-B03-322132  | 2              |
| Gehe/Ichthyol       | Miconazole nitrate | 16E04-B03-322132  | 1              |
| Fagron              | Miconazole nitrate | 16E04-B03-325448  | 1              |
| Fagron              | Miconazole nitrate | 16E04-B03-327362  | 1              |
| Gehe                | Miconazole nitrate | 16E04-B03-327362  | 1              |
| Euro OTC            | Miconazole nitrate | 1705039-01        | 1              |
| Fagron              | Miconazole nitrate | 19051402          | 1              |

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| <b>Supplier</b>            | <b>Substance</b>   | <b>Batch</b>    | <b>Spectra</b> |
|----------------------------|--------------------|-----------------|----------------|
| Fagron                     | Miconazole nitrate | 2900/03/16      | 1              |
| Fagron                     | Miconazole nitrate | 2900/04/14      | 3              |
| Caelo                      | Miconazole nitrate | 2900/10/14      | 1              |
| Caelo                      | Miconazole nitrate | 2900/11/15      | 3              |
| Fagron                     | Miconazole nitrate | 2900/15/13      | 2              |
| Fagron                     | Miconazole nitrate | 2900/16/14      | 2              |
| Fagron                     | Miconazole nitrate | 29000414        | 1              |
| Caelo                      | Miconazole nitrate | 29001614        | 1              |
| Alliance H.                | Miconazole nitrate | 5137910         | 1              |
| Caelo                      | Miconazole nitrate | 8/AKD4          | 1              |
| Sanacorp                   | Miconazole nitrate |                 | 1              |
| Caelo                      | Miconazole nitrate | 4061304         | 1              |
| Caelo                      | Miconazole nitrate | 9177904         | 1              |
| Fagron                     | Miconazole nitrate | 4111301         | 1              |
| Caelo                      | Miconazole nitrate | 1/AD1           | 1              |
| Caelo                      | Miconazole nitrate | 11104103        | 2              |
| Caelo                      | Miconazole nitrate | 11104113        | 3              |
| Caelo                      | Miconazole nitrate | 11104108        | 1              |
| Gehe                       | Miconazole nitrate | 11104114        | 1              |
| Caelo                      | Miconazole nitrate | 11104114        | 1              |
| Caelo                      | Miconazole nitrate | 11243803        | 1              |
| Caelo                      | Miconazole nitrate | 11324901        | 2              |
| Herbasinica                | Miconazole nitrate | 11324901        | 1              |
| sanacorp                   | Miconazole nitrate | 11324902        | 1              |
| Caelo                      | Miconazole nitrate | 11324902        | 1              |
| Caesar & Loretz GmbH, 4... | Miconazole nitrate | 11324904        | 1              |
| Caelo                      | Miconazole nitrate | 11324905        | 5              |
| Phoenix, 13.08.2012        | Miconazole nitrate | 11324905        | 1              |
| Caelo                      | Miconazole nitrate | 11324909        | 2              |
| Caelo                      | Miconazole nitrate | 11324912        | 2              |
| Caelo                      | Miconazole nitrate | 12243801        | 3              |
| Caelo                      | Miconazole nitrate | 11324913        | 1              |
| Anzag, 24.10.2012          | Miconazole nitrate | 11324913        | 1              |
| Fagron                     | Miconazole nitrate | 12/21-M03       | 1              |
| Sanacorp                   | Miconazole nitrate | 12243801        | 1              |
| Caelo                      | Miconazole nitrate | 12243802        | 4              |
| Anzag                      | Miconazole nitrate | 12243802        | 1              |
| Großhandel                 | Miconazole nitrate | 12243803        | 1              |
| Sanacorp                   | Miconazole nitrate | 12243803        | 2              |
| Caelo                      | Miconazole nitrate | 12243805        | 6              |
| Kehr                       | Miconazole nitrate | 12243805        | 1              |
| Caesar und Loretz          | Miconazole nitrate | 12243805        | 1              |
| Großhandel                 | Miconazole nitrate | 12243806        | 1              |
| Caesar&Loretz GmbH D-4...  | Miconazole nitrate | 12243808        | 1              |
| Caelo                      | Miconazole nitrate | 12243806        | 1              |
| Caelo                      | Miconazole nitrate | 12243808        | 8              |
| Fagron                     | Miconazole nitrate | 12243808        | 2              |
| Caesar&loretz,Phoenix      | Miconazole nitrate | 12374301        | 1              |
| Caelo                      | Miconazole nitrate | 12374301        | 3              |
| Alliance Healthcare        | Miconazole nitrate | 12374307        | 1              |
| Caelo                      | Miconazole nitrate | 12374308        | 6              |
| Großhandel                 | Miconazole nitrate | 12374308        | 1              |
| Noweda                     | Miconazole nitrate | 12A16-N02       | 5              |
| Fagron                     | Miconazole nitrate | 12A16-N02       | 3              |
| Bionorica /Phönix          | Miconazole nitrate | 12C13B03-279593 | 1              |
| Fagron                     | Miconazole nitrate | 12H10-N02       | 6              |
| Klenk                      | Miconazole nitrate | 12h10-n02       | 1              |
| Noweda                     | Miconazole nitrate | 12K02-N06       | 3              |
| Caelo                      | Miconazole nitrate | 12k02n06        | 1              |
| Euro OTC                   | Miconazole nitrate | 1307025-01      | 2              |

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| Supplier                   | Substance          | Batch             | Spectra |
|----------------------------|--------------------|-------------------|---------|
| Caelo                      | Miconazole nitrate | 13185601          | 8       |
| Fagron                     | Miconazole nitrate | 13091R            | 1       |
| Fagron                     | Miconazole nitrate | 1316Q-03451       | 1       |
| Caelo                      | Miconazole nitrate | 13185602          | 5       |
| Herstellung                | Miconazole nitrate | 13185602          | 1       |
| Caesar & Loretz GmbH, 4... | Miconazole nitrate | 13185602          | 1       |
| Caelo                      | Miconazole nitrate | 13185603          | 15      |
| Caesar&Loretz GmbH/Anzag   | Miconazole nitrate | 13185603          | 1       |
| Caelo                      | Miconazole nitrate | 13185611          | 14      |
| 20; 04.12.13               | Miconazole nitrate | 13185611          | 2       |
| Fagron                     | Miconazole nitrate | 1328-N06          | 1       |
| Sanacorp                   | Miconazole nitrate | 13352801          | 1       |
| Alliance Health 05.02.2... | Miconazole nitrate | 13352801          | 3       |
| Phoenix                    | Miconazole nitrate | 13352801          | 1       |
| Fagron                     | Miconazole nitrate | 13A14-B09         | 2       |
| Fagron                     | Miconazole nitrate | 13A14B09283005    | 1       |
| Fagron                     | Miconazole nitrate | 13A14-B09-287453  | 1       |
| Fagron                     | Miconazole nitrate | 13A14B09287487    | 1       |
| Fagron                     | Miconazole nitrate | 13d22-n14         | 1       |
| Fagron                     | Miconazole nitrate | 13D22-N14         | 14      |
| Caelo                      | Miconazole nitrate | 13D22-N14         | 2       |
| Fagron                     | Miconazole nitrate | 13E13-N04         | 2       |
| Fagron                     | Miconazole nitrate | 13E13-N08         | 2       |
| Fagron                     | Miconazole nitrate | 13H28N06          | 1       |
| Caelo                      | Miconazole nitrate | 13H28-N06         | 1       |
| Phönix                     | Miconazole nitrate | 13H28-N06         | 1       |
| Fagron                     | Miconazole nitrate | 13H28-N06         | 2       |
| Caelo                      | Miconazole nitrate | 14B18-B02         | 1       |
| Fagron                     | Miconazole nitrate | 14B18-B02-291250  | 1       |
| Fagron                     | Miconazole nitrate | 14D25-B06294959   | 1       |
| Fagron                     | Miconazole nitrate | 15/08-B07-314838  | 1       |
| Fagron                     | Miconazole nitrate | 15I08-B07-3144838 | 1       |
| Fagron                     | Miconazole nitrate | 17011307          | 1       |
| Fagron                     | Miconazole nitrate | 20081201          | 1       |
| Caelo                      | Miconazole nitrate | 28051306          | 1       |
| Fagron                     | Miconazole nitrate | 27061202          | 1       |
| Fagron                     | Miconazole nitrate | 2900/08/12        | 4       |
| Fagron                     | Miconazole nitrate | 31101306          | 1       |
| Fagron                     | Miconazole nitrate | 2900/10/14        | 1       |
| Caelo                      | Miconazole nitrate | 411092-2-P        | 1       |
| Caelo                      | Miconazole nitrate | 80644099          | 1       |
| Caelo                      | Miconazole nitrate | AKD9              | 1       |
| Caelo                      | Miconazole nitrate | 1307025-02        | 1       |
| Fagron                     | Miconazole nitrate | 14b18-b02-291247  | 1       |
| Fargon                     | Miconazole nitrate | 14D25-B06-294959  | 1       |
| Caelo                      | Miconazole nitrate | P143/14           | 1       |
| EUro/AHD                   | Miconazole nitrate | 12243808          | 1       |
| Anzag                      | Miconazole nitrate | 12374301          | 3       |
| AHD                        | Miconazole nitrate | 12374307          | 1       |

- 68 872 spectra from 414 *Apo-Ident* customers from a total of 23 603 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Miconazole nitrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Miconazole nitrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 284           | 0              | 71 102        |
| Type B | 0              | 675           | 23             | 146 031       |
| Type C | 0              | 753           | 8              | 68 872        |

The substance/substance group *Miconazole nitrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.8873 %) |
| Type B | 100.0000 % (> 99.9923 %) | 96.7049 % (> 96.2751 %)  |
| Type C | 100.0000 % (> 99.8812 %) | 98.9488 % (> 98.5545 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20817     | 21900               | 1.10                         | 33.13                           |
| 20875     | 22630               | 5.13                         | 28.52                           |
| 21350     | 21350               | 0.00                         | 28.43                           |
| 21649     | 21350               | 5.12                         | 27.45                           |
| 21900     | 21900               | 0.00                         | 32.75                           |
| 22630     | 22630               | 0.00                         | 31.54                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Minoxidil**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20879-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Minoxidil; Minoxidilum

### Special notes

When selecting the *Minoxidil* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Minoxidil*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate        |
|----------|-----------|------------|-----------|---------|--------------------|
| Caelo    | Minoxidil | 13039501   | 20879     | 40      | 20130306           |
| Caelo    | Minoxidil | 14093701   | 21359     | 40      | 20140428           |
| Euro OTC | Minoxidil | 1311038-01 | 21630     | 40      | AR-15-FG-007848-01 |
| Euro OTC | Minoxidil | 1411006-01 | 21912     | 40      | 20141210           |
| Euro OTC | Minoxidil | 1509035    | 21933     | 40      | 20151016*          |
| Euro OTC | Minoxidil | 1602013    | 22365     | 40      | 20160225*          |
| Euro OTC | Minoxidil | 1612011    | 22982     | 40      | 20170130*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 280 spectra of 7 reference samples from the substance/substance group *Minoxidil*. These samples are listed above in the [calibration samples](#) section.
- 71 106 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 419 spectra of 11 reference samples from the substance/substance group *Minoxidil*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Caelo    | Minoxidil | 14093701   | 21361              | 40      |
| Euro OTC | Minoxidil | 1311038-01 | 21630 <sup>†</sup> | 19      |
| Euro OTC | Minoxidil | 1411006-01 | 21912 <sup>†</sup> | 20      |
| Euro OTC | Minoxidil | 1509035    | 21933 <sup>†</sup> | 20      |
| Euro OTC | Minoxidil | 1602013    | 22365 <sup>†</sup> | 20      |
| Euro OTC | Minoxidil | 1607007    | 22688              | 40      |
| Euro OTC | Minoxidil | 1705008    | 23437              | 40      |
| Euro OTC | Minoxidil | 1411006-01 | 21912SI            | 60      |
| Euro OTC | Minoxidil | 1509035    | 21933SI            | 60      |
| Euro OTC | Minoxidil | 1602013    | 22365SI            | 60      |
| Euro OTC | Minoxidil | 1612011    | 22982SI            | 40      |

- 146 310 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 873 spectra from 213 *Apo-Ident* customers from 222 batches from the substance/substance group *Minoxidil*.

| Supplier                    | Substance | Batch      | Spectra |
|-----------------------------|-----------|------------|---------|
| Bombastus                   | Minoxidil | 4/13       | 1       |
| Euro OTC                    | Minoxidil | 4/13       | 2       |
| icrom spa                   | Minoxidil | 511v       | 1       |
| ICROM                       | Minoxidil | 6/12       | 1       |
| Euro OTC                    | Minoxidil | 6/12       | 1       |
| Fagron                      | Minoxidil | 7/13       | 2       |
| Euro OTC                    | Minoxidil | 10/13      | 1       |
| Caelo                       | Minoxidil | 5081502    | 1       |
| Audor Pharma                | Minoxidil | 414E-02844 | 1       |
| Fagron                      | Minoxidil | 15/13      | 1       |
| Fagron                      | Minoxidil | 612212844  | 1       |
| Euro OTC                    | Minoxidil | 6614849    | 1       |
| Euro OTC                    | Minoxidil | 1009042-01 | 3       |
| Fagron                      | Minoxidil | 10J14-N19  | 1       |
| Euro OTC                    | Minoxidil | 104029-02  | 1       |
| Fagron                      | Minoxidil | 11021402   | 1       |
| Euro OTC                    | Minoxidil | 1102010-02 | 1       |
| EuRho                       | Minoxidil | 1105030-02 | 1       |
| EuRho                       | Minoxidil | 1108039-02 | 2       |
| Euro OTC                    | Minoxidil | 1108039-03 | 1       |
| Fagron                      | Minoxidil | 111012010  | 1       |
| Euro OTC                    | Minoxidil | 1112024-01 | 3       |
| Euro OTC                    | Minoxidil | 1112024-02 | 7       |
| Caelo                       | Minoxidil | 1112024-01 | 1       |
| Anzag                       | Minoxidil | 1112024-02 | 1       |
| Euro OTC                    | Minoxidil | 1112024-03 | 6       |
| Phönix                      | Minoxidil | 1112024-03 | 1       |
| Fiebig ek: 36.06EUR 31.0812 | Minoxidil | 111202403  | 1       |
| Caelo                       | Minoxidil | 11150207   | 2       |
| Bombastus                   | Minoxidil | 1112024-03 | 1       |
| Euro/Gehe                   | Minoxidil | 1112024-03 | 1       |
| Caelo                       | Minoxidil | 11150209   | 1       |
| Caelo                       | Minoxidil | 11302003   | 2       |
| Caelo                       | Minoxidil | 11302005   | 1       |
| Post-Apotheke               | Minoxidil | 11302005   | 2       |
| Fagron                      | Minoxidil | 11e17-n07  | 1       |
| Fagron                      | Minoxidil | 11E17-N07  | 3       |
| Fagron                      | Minoxidil | 11K11-N09  | 3       |
| Caelo                       | Minoxidil | 12023901   | 3       |
| Phoenix 21.02.2013          | Minoxidil | 12023901   | 1       |
| Sanacorp                    | Minoxidil | 120056-01  | 1       |
| Caelo                       | Minoxidil | 12023902   | 2       |
| Caelo                       | Minoxidil | 12023907   | 6       |
| Caelo                       | Minoxidil | 12023908   | 2       |
| Caelo                       | Minoxidil | 1203035    | 1       |
| Euro OTC                    | Minoxidil | 1203035    | 1       |
| Euro OTC                    | Minoxidil | 1203035-0  | 1       |
| Euro OTC                    | Minoxidil | 1203035-01 | 12      |
| Euro OTC                    | Minoxidil | 120303501  | 2       |
| Icrom Spa                   | Minoxidil | 1203035-01 | 1       |
| Anzag 18.10.12 ek:40,14     | Minoxidil | 1203035-01 | 1       |
| Anzag 14.11.12 ek:40,14     | Minoxidil | 120303501  | 1       |

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| Supplier                    | Substance | Batch             | Spectra |
|-----------------------------|-----------|-------------------|---------|
| Sanacorp                    | Minoxidil | 1203035-01        | 1       |
| Euro OTC                    | Minoxidil | 1203035-02        | 8       |
| Euro OTC                    | Minoxidil | 120303502         | 1       |
| Phönix                      | Minoxidil | 1203035-02        | 2       |
| Euro OTC                    | Minoxidil | 1203035-03        | 13      |
| Caelo                       | Minoxidil | 120303503         | 1       |
| Fagron                      | Minoxidil | 120303503         | 1       |
| Euro OTC                    | Minoxidil | 120303503         | 1       |
| Anzag 07.02.13 ek: 40,14EUR | Minoxidil | 120303503         | 1       |
| Alliance Healthc. 15.05...  | Minoxidil | 1203035-03        | 1       |
| Euro OTC                    | Minoxidil | 12100056-01       | 1       |
| Euro OTC                    | Minoxidil | 12100560          | 1       |
| Sanacorp                    | Minoxidil | 1210056-01        | 1       |
| Euro OTC                    | Minoxidil | 1210056-01        | 17      |
| Alliance Healthcare         | Minoxidil | 1210056-01        | 1       |
| Europharm/Sanacorp          | Minoxidil | 1210056-01        | 1       |
| Caelo                       | Minoxidil | 1210056-01        | 2       |
| Euro OTC                    | Minoxidil | 121005601         | 1       |
| AHD                         | Minoxidil | 1210056-01        | 1       |
| Caelo                       | Minoxidil | 121005601         | 1       |
| Euro OTC                    | Minoxidil | 1210056-02        | 27      |
| Caelo                       | Minoxidil | 1210056-02        | 3       |
| Alliance Healthcare         | Minoxidil | 1210056-02        | 1       |
| Sanacorp                    | Minoxidil | 1210056-02        | 2       |
| AHC 14.08.13 EK40,14        | Minoxidil | 1210056-02        | 1       |
| Caelo                       | Minoxidil | 12273703          | 2       |
| Caelo                       | Minoxidil | 12273704          | 5       |
| Caelo                       | Minoxidil | 12273710          | 1       |
| Gehe 02.07.2013             | Minoxidil | 123039503         | 1       |
| Fagron                      | Minoxidil | 12A25-N04         | 5       |
| Fagron                      | Minoxidil | 12C29-N050087/240 | 1       |
| Fagron                      | Minoxidil | 12C29-N05         | 5       |
| Klenk                       | Minoxidil | 12c29-n05         | 1       |
| Fagron                      | Minoxidil | 12C29-N050145/240 | 1       |
| Noweda                      | Minoxidil | 12C29-N05         | 1       |
| Hedinger/Sanacorp           | Minoxidil | 12C29-N05         | 1       |
| Fagron                      | Minoxidil | 12H07-N03         | 22      |
| Fagron                      | Minoxidil | 12H07N03          | 1       |
| Fagron                      | Minoxidil | 12H07-No3         | 1       |
| Fagron                      | Minoxidil | 12H07-N030265/432 | 1       |
| Fagron                      | Minoxidil | 12H07-N03         | 1       |
| Fagron                      | Minoxidil | 12H07-N03         | 1       |
| Caelo                       | Minoxidil | 13/23-N07         | 1       |
| Caelo                       | Minoxidil | 13039501          | 9       |
| Caesar & Loretz GmbH        | Minoxidil | 13039501          | 1       |
| Caelo                       | Minoxidil | 13039503          | 3       |
| Alliance Health 04.11.2...  | Minoxidil | 13039503          | 1       |
| Euro OTC                    | Minoxidil | 1304029-01        | 18      |
| euroct/Gehe                 | Minoxidil | 1304029-01        | 1       |
| Phönix                      | Minoxidil | 1304029-01        | 1       |
| Caelo                       | Minoxidil | 130402901         | 1       |
| Euro OTC                    | Minoxidil | 130402901         | 1       |
| Apotärze                    | Minoxidil | 1304029-02        | 3       |
| EuRho / Noweda              | Minoxidil | 1304029-02        | 1       |
| Euro OTC                    | Minoxidil | 1304029-02        | 16      |
| Euro OTC                    | Minoxidil | 130402902         | 1       |
| Caelo                       | Minoxidil | 1304029-02        | 1       |
| Euro                        | Minoxidil | 1304029-02        | 1       |
| Caelo                       | Minoxidil | 130402902         | 1       |
| Sanacorp                    | Minoxidil | 1304029-02        | 1       |

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| Supplier                   | Substance | Batch            | Spectra |
|----------------------------|-----------|------------------|---------|
| Euro OTC                   | Minoxidil | 1311038-01       | 32      |
| Caelo                      | Minoxidil | 1309501          | 1       |
| Euro OTC                   | Minoxidil | 1304029-C2       | 1       |
| GEHE 07.05.2014            | Minoxidil | 1311038-01       | 2       |
| Caelo                      | Minoxidil | 1311038-01       | 3       |
| Euro OTC                   | Minoxidil | 131103801        | 4       |
| AHD                        | Minoxidil | 1311038-01       | 1       |
| Ichthyol-Gesellschaft      | Minoxidil | 1311038-01       | 1       |
| Fagron                     | Minoxidil | 1311038-01       | 1       |
| Sanacorp                   | Minoxidil | 13179501         | 2       |
| Caelo                      | Minoxidil | 13179501         | 7       |
| Euro OTC                   | Minoxidil | 131138-01        | 1       |
| Euro OTC                   | Minoxidil | 13110838-01      | 1       |
| Sanacorp                   | Minoxidil | 13179502         | 2       |
| Caelo                      | Minoxidil | 13179502         | 8       |
| Caelo                      | Minoxidil | 13179503         | 7       |
| Alliance Health 30.04.2... | Minoxidil | 13179503         | 2       |
| Caelo                      | Minoxidil | 13179504         | 2       |
| Caelo                      | Minoxidil | 13179507         | 2       |
| Caelo                      | Minoxidil | 13373106         | 2       |
| Fagron                     | Minoxidil | 13E13-N10        | 17      |
| Anzag                      | Minoxidil | 13E13-N10        | 1       |
| Fargron                    | Minoxidil | 13E13-N10        | 2       |
| Doppeleiche Apotheke       | Minoxidil | 13E13-N10        | 2       |
| Fagron                     | Minoxidil | 13E13N10         | 1       |
| Caelo                      | Minoxidil | 13E13-N10        | 1       |
| Fagron                     | Minoxidil | 13H07-N03        | 1       |
| Fagron                     | Minoxidil | 13I23-N07        | 11      |
| Caelo                      | Minoxidil | 13I23-N07        | 2       |
| Fagron                     | Minoxidil | 13J23N07         | 2       |
| Fagron                     | Minoxidil | 13J29-B02        | 1       |
| Fagron                     | Minoxidil | 13K04-B05-0004   | 1       |
| Fagron                     | Minoxidil | 13K04-B05-290377 | 5       |
| Fagron                     | Minoxidil | 13K04-B05-290379 | 2       |
| Fagron                     | Minoxidil | 13K04-B05-290380 | 4       |
| Caelo                      | Minoxidil | 13K04B05290380   | 1       |
| Fagron                     | Minoxidil | 13123-N07        | 1       |
| Euro OTC                   | Minoxidil | 14050281         | 1       |
| Euro OTC                   | Minoxidil | 140502801        | 3       |
| Euro OTC                   | Minoxidil | 1405028-01       | 30      |
| sanacorp                   | Minoxidil | 1405028-01       | 1       |
| Sanacorp                   | Minoxidil | 1405028-01       | 1       |
| Euro/ Phönix               | Minoxidil | 1405028-01       | 1       |
| Gehe                       | Minoxidil | 1405028-01       | 1       |
| Caelo                      | Minoxidil | 1405028-01       | 2       |
| Sanacorp                   | Minoxidil | 140502801        | 1       |
| Euro OTC                   | Minoxidil |                  | 2       |
| Euro OTC                   | Minoxidil | 1405028-1        | 1       |
| Sanacorp                   | Minoxidil | 14093701         | 1       |
| Euro/Gehe                  | Minoxidil | 140528-01        | 1       |
| Euro OTC                   | Minoxidil | 140528-01        | 1       |
| Caelo                      | Minoxidil | 14093702         | 2       |
| Sanacorp                   | Minoxidil | 14093702         | 1       |
| Caelo                      | Minoxidil | 14093703         | 5       |
| Noweda                     | Minoxidil | 14093703         | 1       |
| Caelo                      | Minoxidil | 14093706         | 2       |
| Caelo                      | Minoxidil | 14093707         | 1       |
| Caelo                      | Minoxidil | 1411006-01       | 2       |
| Euro OTC                   | Minoxidil | 1411006-01       | 32      |
| Alliance health            | Minoxidil | 1411006-01       | 3       |

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| <b>Supplier</b> | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|-----------------|------------------|-------------------|----------------|
| Euro OTC        | Minoxidil        | 141100601         | 5              |
| Fagron          | Minoxidil        | 1411006-01        | 1              |
| Euro/Phönix     | Minoxidil        | 1411006-01        | 1              |
| Caelo           | Minoxidil        | 14234505          | 5              |
| Caelo           | Minoxidil        | 14234502          | 2              |
| Euro OTC        | Minoxidil        | 1411006601        | 1              |
| Fagron          | Minoxidil        | 1420001962        | 1              |
| Caelo           | Minoxidil        | 14234509          | 3              |
| Fagron          | Minoxidil        | 14B04-B07         | 1              |
| Fagron          | Minoxidil        | 14B04-B07-290883  | 4              |
| Fagron          | Minoxidil        | 14L03-B02         | 2              |
| Fagron          | Minoxidil        | 14B04-B07-297364  | 1              |
| Fagron          | Minoxidil        | 14L03-B02-301429  | 6              |
| Fagron          | Minoxidil        | 14L03-B02301429   | 1              |
| Fagron          | Minoxidil        | 14L03-B02-301430  | 2              |
| Fagron          | Minoxidil        | 14L03-B02-301431  | 1              |
| Fagron          | Minoxidil        | 15F02B09          | 1              |
| Caelo           | Minoxidil        | 14L03-B02-301432  | 1              |
| Fagron          | Minoxidil        | 14L03-B02-301541  | 1              |
| Fagron          | Minoxidil        | 14L03-B02-301430  | 1              |
| Euro OTC        | Minoxidil        | 150401-01         | 1              |
| Euro OTC        | Minoxidil        | 1504013-01        | 27             |
| Sanacorp        | Minoxidil        | 1504013-01        | 1              |
| Caelo           | Minoxidil        | 1504013-01        | 5              |
| Euro            | Minoxidil        | 1504013-01        | 2              |
| Euro OTC        | Minoxidil        | 1504013-02        | 21             |
| AHD             | Minoxidil        | 1504013-02        | 1              |
| Euro OTC        | Minoxidil        | 1504013-2         | 1              |
| Euro OTC        | Minoxidil        | 1509035-01        | 18             |
| Caelo           | Minoxidil        | 1509035-01        | 1              |
| Euro/Anzag      | Minoxidil        | 150903501         | 1              |
| Fagron          | Minoxidil        | 1520000768        | 3              |
| Caelo           | Minoxidil        | 1520002455        | 1              |
| Caelo           | Minoxidil        | 15230802          | 3              |
| Caelo           | Minoxidil        | 15230803          | 1              |
| Caelo           | Minoxidil        | 15230804          | 2              |
| Caelo           | Minoxidil        | 15230805          | 2              |
| Caelo           | Minoxidil        | 15230811          | 4              |
| Caelo           | Minoxidil        | 15436201          | 3              |
| Gehe            | Minoxidil        | 15436201          | 1              |
| Caelo           | Minoxidil        | 15436202          | 5              |
| Sanacorp        | Minoxidil        | 15436202          | 1              |
| Caelo           | Minoxidil        | 15436404          | 2              |
| Caelo           | Minoxidil        | 15436204          | 1              |
| Gehe            | Minoxidil        | 15436406          | 1              |
| Caelo           | Minoxidil        | 15436408          | 1              |
| Fagron          | Minoxidil        | 15E19-06-308183   | 1              |
| Fagron          | Minoxidil        | 15E19-B06         | 2              |
| Fagron          | Minoxidil        | 15E19-B06-308179  | 1              |
| Fagron          | Minoxidil        | 15E19-b06-308180  | 1              |
| Fagron          | Minoxidil        | 15E19-B06-308180  | 1              |
| Fagron          | Minoxidil        | 15E19-B06-308181  | 2              |
| Fagron          | Minoxidil        | 15E19-B06-308182  | 1              |
| Fagron          | Minoxidil        | 15E-19-B06-308182 | 1              |
| Caelo           | Minoxidil        | 15E19-B06-308183  | 1              |
| Fagron          | Minoxidil        | 15E19-B06-308183  | 2              |
| Fagron          | Minoxidil        | 15E19-B06-308183  | 1              |
| Fagron          | Minoxidil        | 15H07-B03         | 2              |
| Fagron          | Minoxidil        | 15H07-B01-314726  | 1              |
| Fagron          | Minoxidil        | 15F02-B08         | 1              |

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| Supplier     | Substance | Batch            | Spectra |
|--------------|-----------|------------------|---------|
| Fagron       | Minoxidil | 15K17-B05-318241 | 1       |
| Fagron       | Minoxidil | 15K17-B06        | 1       |
| Fagron       | Minoxidil | 15K17-B05-318691 | 1       |
| Fagron       | Minoxidil | 15K17-B05-318240 | 1       |
| Fagron       | Minoxidil | 15K17-B05-320188 | 1       |
| Caelo        | Minoxidil | 15K17-B06-321926 | 1       |
| Fagron       | Minoxidil | 15K17-B06-321926 | 1       |
| Fagron       | Minoxidil | 15K17-B06-324965 | 1       |
| Fagron       | Minoxidil | 15K17-B06-325490 | 1       |
| Caelo        | Minoxidil | 160013-01        | 1       |
| Euro OTC     | Minoxidil | 1602013-01       | 19      |
| Caelo        | Minoxidil | 1602013-01       | 6       |
| Gehe         | Minoxidil | 1602013-01       | 1       |
| Icrom/Gehe   | Minoxidil | 1602013-01       | 1       |
| Phoenix      | Minoxidil | 1602013-02       | 1       |
| Euro OTC     | Minoxidil | 1602013-02       | 6       |
| Caelo        | Minoxidil | 1602013-02       | 3       |
| Caelo        | Minoxidil | 160201302        | 1       |
| Euro/Noweda  | Minoxidil | 1602013-02       | 1       |
| Euro OTC     | Minoxidil | 1607007-01       | 12      |
| Euro OTC     | Minoxidil | 1607007          | 1       |
| Euro OTC     | Minoxidil | 1602013-1        | 1       |
| Euro OTC     | Minoxidil | 16070007-01      | 1       |
| Caelo        | Minoxidil | 1607007-01       | 2       |
| EuRho/Noweda | Minoxidil | 1607007-01       | 1       |
| Euro/Phönix  | Minoxidil | 161201101        | 2       |
| Euro OTC     | Minoxidil | 1612011          | 1       |
| Euro OTC     | Minoxidil | 1612011-01       | 9       |
| Phönix       | Minoxidil | 1612011-01       | 1       |
| Gehe         | Minoxidil | 1612011-01       | 1       |
| Caelo        | Minoxidil | 17011602         | 1       |
| Fagron       | Minoxidil | 16J24-B04        | 1       |
| Fagron       | Minoxidil | 17B22-B01        | 1       |
| Fagron       | Minoxidil | 17B22-B01-334447 | 1       |
| Euro OTC     | Minoxidil | 2002312844       | 1       |
| Caelo        | Minoxidil | 22031402         | 1       |
| Caelo        | Minoxidil | 20151112-5       | 1       |
| Caelo        | Minoxidil | 20160211-1       | 1       |
| Caelo        | Minoxidil | 240813001        | 1       |
| Fagron       | Minoxidil | 26021303         | 1       |
| Fagron       | Minoxidil | 26111302         | 1       |
| phönix       | Minoxidil |                  | 1       |
| Caelo        | Minoxidil | 240912010        | 1       |
| Euro OTC     | Minoxidil | 29071402         | 1       |
| Fagron       | Minoxidil | 27081301         | 1       |
| Caelo        | Minoxidil | 2905047-01       | 1       |
| Caelo        | Minoxidil | 31051305         | 1       |
| Caelo        | Minoxidil | 2913A-02844      | 1       |
| Caelo        | Minoxidil | 3013M-02844      | 2       |
| Fagron       | Minoxidil | 4110I-02844      | 1       |
| Euro OTC     | Minoxidil | 700158           | 1       |
| Audor Pharma | Minoxidil | AP001/11M        | 1       |
| Audor Pharma | Minoxidil | AP001/16M        | 4       |
| Gehe         | Minoxidil | AP006/13M        | 1       |
| Audor Pharma | Minoxidil | AP006/13M        | 2       |
| Audor Pharma | Minoxidil | AP007/15M        | 3       |
| Audor Pharma | Minoxidil | AP008/14M        | 6       |
| Audor Pharma | Minoxidil | AP010/12M        | 6       |
| Audor Pharma | Minoxidil | AP016/15M        | 5       |
| Audor Pharma | Minoxidil | AP011/16M        | 1       |

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| Supplier                    | Substance | Batch               | Spectra |
|-----------------------------|-----------|---------------------|---------|
| Audor Pharma                | Minoxidil | AP020/11M           | 5       |
| Audor Pharma                | Minoxidil | AP23601ML           | 1       |
| Audor Pharma                | Minoxidil |                     | 1       |
| Caelo                       | Minoxidil | AP011/16M           | 1       |
| Audor Pharma                | Minoxidil | AP012/16M           | 1       |
| Audor Pharma                | Minoxidil | AP-016/15M          | 1       |
| Audor Pharma                | Minoxidil | AP088/14M           | 1       |
| Caelo                       | Minoxidil |                     | 4       |
| apo-ident                   | Minoxidil | Euro-OTC            | 1       |
| Fagron                      | Minoxidil | Fagron              | 1       |
| Vdl 14.07.14                | Minoxidil | 1311038-01          | 1       |
| Hedinger                    | Minoxidil | 14B04-B07           | 2       |
| Sanacorp, 81,00EUR, 27.1.17 | Minoxidil | 1607007-01          | 1       |
| apo-ident.                  | Minoxidil | 1607007-07          | 1       |
| Euro OTC                    | Minoxidil | 1108039-01          | 1       |
| Noweda                      | Minoxidil | 11150207            | 1       |
| GEHE                        | Minoxidil | 11302003            | 1       |
| Caelo                       | Minoxidil | 11K11-n09           | 1       |
| Caelo                       | Minoxidil | 1203035-01          | 1       |
| EUro/AHD                    | Minoxidil | 1203035-03          | 2       |
| A.H.D                       | Minoxidil | 1210056-01          | 1       |
| Fagron                      | Minoxidil | 1210056-02          | 1       |
| Caelo                       | Minoxidil | 12H07-N03           | 4       |
| Euro OTC                    | Minoxidil | 13001               | 1       |
| Caelo                       | Minoxidil | 13179501-3467312121 | 1       |

- 68 760 spectra from 414 *Apo-Ident* customers from a total of 23 584 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Minoxidil* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Minoxidil* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 254           | 26             | 71 106        |
| <b>Type B</b> | 0              | 411           | 8              | 146 310       |
| <b>Type C</b> | 0              | 858           | 15             | 68 760        |

The substance/substance group *Minoxidil* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate        |
|---------------|--------------------------|-------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 90.7143 % (> 89.6429 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 98.0907 % (> 97.3747 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 98.2818 % (> 97.9381 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20879     | 22365               | 1.69                         | 32.85                           |
| 21359     | 21933               | 4.26                         | 33.61                           |
| 21630     | 21630               | 0.00                         | 33.33                           |
| 21912     | 21933               | 3.39                         | 34.29                           |
| 21933     | 21933               | 0.00                         | 32.33                           |
| 22365     | 22365               | 0.00                         | 31.60                           |
| 22982     | 22982               | 0.00                         | 33.04                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Mometasone furoate, micronized**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20100-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Mometasone furoate, micronized; Mometasoni furoas micronisatum; Mometasonum furanicum micronisatum

### Special notes

When selecting the *Mometasone furoate, micronized* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Mometasone furoate, micronized*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Fagron   | Mometasone furoa... | 13F17-N01  | 20850     | 30      | 20130620    |
| Euro OTC | Mometasone furoa... | 1403015-01 | 21602     | 40      | 20140503    |
| Euro OTC | Mometasone furoa... | 1510036    | 22238     | 40      | 20151118*   |
| Caelo    | Mometasone furoa... | 160286     | 22433     | 40      | 20160316*   |

*continued on the next page*

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Mometasone furoa... | 16A20-B06-319750 | 22887     | 40      | 20160209    |
| Euro OTC | Mometasone furoa... | 1610009          | 23136     | 40      | 20170321*   |
| Fagron   | Mometasone furoa... | 13F17-N01        | 20850SI   | 29      | 20130620    |
| Euro OTC | Mometasone furoa... | 1403015-01       | 21602SI   | 21      | 20140503    |
| Euro OTC | Mometasone furoa... | 1510036          | 22238SI   | 20      | 20151118*   |
| Fagron   | Mometasone furoa... | 16A20-B06-319750 | 22887SI   | 30      | 20160209    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 330 spectra of 10 reference samples from the substance/substance group *Mometasone furoate, micronized*. These samples are listed above in the [calibration samples](#) section.
- 71 056 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 419 spectra of 15 reference samples from the substance/substance group *Mometasone furoate, micronized*.

| Supplier | Substance                      | Batch      | Sample ID            | Spectra |
|----------|--------------------------------|------------|----------------------|---------|
| Fagron   | Mometasone furoate, micronized | 9F22-N05   | 20100                | 40      |
| Caelo    | Mometasone furoate, micronized | 13304605   | 21374                | 60      |
| Euro OTC | Mometasone furoate, micronized | 1403015-01 | 21602 <sup>†</sup>   | 20      |
| Euro OTC | Mometasone furoate, micronized | 1510036    | 22238 <sup>†</sup>   | 20      |
| Caelo    | Mometasone furoate, micronized | 160286     | 22433 <sup>†</sup>   | 20      |
| Euro OTC | Mometasone furoate, micronized | 1606021    | 22715                | 40      |
| Caelo    | Mometasone furoate, micronized | 163532     | 23046                | 40      |
| Fagron   | Mometasone furoate, micronized | 13F17-N01  | 20850SI <sup>†</sup> | 15      |
| Caelo    | Mometasone furoate, micronized | 13304605   | 21374SI              | 38      |
| Euro OTC | Mometasone furoate, micronized | 1403015-01 | 21602SI <sup>†</sup> | 10      |
| Euro OTC | Mometasone furoate, micronized | 1510036    | 22238SI <sup>†</sup> | 10      |
| Caelo    | Mometasone furoate, micronized | 160286     | 22433SI              | 30      |
| Euro OTC | Mometasone furoate, micronized | 1606021    | 22715SI              | 33      |
| Caelo    | Mometasone furoate, micronized | 163532     | 23046SI              | 23      |
| Euro OTC | Mometasone furoate, micronized | 1610009    | 23136SI              | 20      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

- 146310 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 530 spectra from 163 *Apo-Ident* customers from 202 batches from the substance/substance group *Mometasone furoate, micronized*.

| Supplier              | Substance                      | Batch            | Spectra |
|-----------------------|--------------------------------|------------------|---------|
| Caelo                 | Mometasone furoate, micronized | 1/AKD15          | 1       |
| Fagron                | Mometasone furoate, micronized | 5/0715           | 1       |
| Sanacorp              | Mometasone furoate, micronized | 1/AKD4           | 1       |
| Fagron                | Mometasone furoate, micronized | 10E31-N26        | 1       |
| Caelo                 | Mometasone furoate, micronized | 11H10-N01        | 1       |
| Fagron                | Mometasone furoate, micronized | 11K28-N09        | 2       |
| Caelo                 | Mometasone furoate, micronized | 12351202         | 4       |
| Caelo                 | Mometasone furoate, micronized | 12351205         | 2       |
| Caelo                 | Mometasone furoate, micronized | 12351208         | 1       |
| Caelo                 | Mometasone furoate, micronized | 12351215         | 4       |
| AHD 20.06.14 EK 37,29 | Mometasone furoate, micronized | 12C07-B05-291268 | 1       |
| Phönix                | Mometasone furoate, micronized | 13/23-N02        | 2       |
| Caelo                 | Mometasone furoate, micronized | 13304604         | 2       |
| Caelo                 | Mometasone furoate, micronized | 13304605         | 5       |
| Caelo                 | Mometasone furoate, micronized | 13304603         | 1       |
| EuRho/Phönix          | Mometasone furoate, micronized | 1307037-01       | 2       |
| Caelo                 | Mometasone furoate, micronized | 13304606         | 2       |
| Caelo                 | Mometasone furoate, micronized | 13304609         | 2       |
| Caelo                 | Mometasone furoate, micronized | 13304612         | 1       |
| Fagron                | Mometasone furoate, micronized | 13D08-N06        | 1       |
| Fagron                | Mometasone furoate, micronized | 13H13-N04        | 12      |
| Fagron                | Mometasone furoate, micronized | 13D08-N06        | 16      |
| Fagron                | Mometasone furoate, micronized | 13J23-N02        | 20      |
| GEHE 17.04.2014       | Mometasone furoate, micronized | 13J23-N02        | 1       |
| Fagron                | Mometasone furoate, micronized | 13j23-N02        | 1       |
| Caelo                 | Mometasone furoate, micronized | 13J23-N02        | 3       |
| Phönix Gotha          | Mometasone furoate, micronized | 1403015-01       | 1       |
| Euro OTC              | Mometasone furoate, micronized | 1403015-01       | 1       |
| Euro OTG              | Mometasone furoate, micronized | 1403015-01       | 1       |
| Euro OTC              | Mometasone furoate, micronized | 1408010-01       | 2       |
| Caelo                 | Mometasone furoate, micronized | 14281102         | 2       |
| Caelo                 | Mometasone furoate, micronized | 14281103         | 1       |
| EuRho                 | Mometasone furoate, micronized | 1408010-01       | 1       |
| Fagron                | Mometasone furoate, micronized | 14C07-B05        | 1       |
| Fagron                | Mometasone furoate, micronized | 14C07-B05-291264 | 1       |
| Hepart AG             | Mometasone furoate, micronized | 14c07-b05-291266 | 2       |
| Fagron                | Mometasone furoate, micronized | 14C07-B05-291266 | 4       |
| Caelo                 | Mometasone furoate, micronized | 14C07-B05-291268 | 9       |
| Fagron                | Mometasone furoate, micronized | 14C07-B05-291268 | 5       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier                 | Substance                      | Batch            | Spectra |
|--------------------------|--------------------------------|------------------|---------|
| Fagron                   | Mometasone furoate, micronized | 14C07B05291268   | 1       |
| Fagron                   | Mometasone furoate, micronized | 14E20-B04        | 5       |
| Fagron                   | Mometasone furoate, micronized | 14e20b04291265   | 1       |
| Fagron                   | Mometasone furoate, micronized | 14E20-B04-291265 | 5       |
| Fagron                   | Mometasone furoate, micronized | 14e20-b04-291265 | 1       |
| Phönix                   | Mometasone furoate, micronized | 14E20-B04-291267 | 1       |
| Caelo                    | Mometasone furoate, micronized | 14E20-B04-291267 | 4       |
| Fagron                   | Mometasone furoate, micronized | 14E20-B04-291267 | 7       |
| Sanacorp                 | Mometasone furoate, micronized | 14E20-B04-291267 | 1       |
| Fagron                   | Mometasone furoate, micronized | 14e20-b04-291267 | 1       |
| Fagron                   | Mometasone furoate, micronized | 14E20-B04-291269 | 2       |
| Fagron                   | Mometasone furoate, micronized | 14E20-B04-294645 | 5       |
| Fagron                   | Mometasone furoate, micronized | 14E20-B04-302374 | 2       |
| Fagron                   | Mometasone furoate, micronized | 14H06-B07297240  | 1       |
| Fagron                   | Mometasone furoate, micronized | 14H06-B07-297240 | 5       |
| Caelo                    | Mometasone furoate, micronized | 14H06-B07298481  | 1       |
| Fagron                   | Mometasone furoate, micronized | 14H06-B07-298481 | 1       |
| Cael Sanacorp 05.02.2016 | Mometasone furoate, micronized | 14H06-B07-298481 | 1       |
| Fagron                   | Mometasone furoate, micronized | 14H06-B07-298482 | 7       |
| Fagron                   | Mometasone furoate, micronized | 14H06-B07-302375 | 1       |
| Fagron                   | Mometasone furoate, micronized | 14H06-B07-302376 | 3       |
| Fagron                   | Mometasone furoate, micronized | 15/11-B02        | 4       |
| Fagron                   | Mometasone furoate, micronized | 15/11-B02-314479 | 4       |
| Fagron                   | Mometasone furoate, micronized | 15/11-B02-31447  | 1       |
| Fagron                   | Mometasone furoate, micronized | 15/11-B02-315705 | 2       |
| Fagron                   | Mometasone furoate, micronized | 15/11-B02-316705 | 1       |
| Caelo                    | Mometasone furoate, micronized | 15/11-Bo2-314479 | 1       |
| Euro OTC                 | Mometasone furoate, micronized | 1504012-01       | 8       |
| Euro OTC                 | Mometasone furoate, micronized | 1504012-02       | 3       |
| Euro OTC                 | Mometasone furoate, micronized | 1510036-01       | 6       |
| Caelo                    | Mometasone furoate, micronized | 1510036-001      | 1       |
| Caelo                    | Mometasone furoate, micronized | 15110301         | 3       |
| Caelo                    | Mometasone furoate, micronized | 15110305         | 3       |
| Fagro                    | Mometasone furoate, micronized | 1511B02          | 1       |
| Caelo                    | Mometasone furoate, micronized | 15189801         | 1       |
| Caelo                    | Mometasone furoate, micronized | 15189802         | 1       |
| Caelo                    | Mometasone furoate, micronized | 15189807         | 5       |
| Caelo                    | Mometasone furoate, micronized | 15189804         | 2       |
| Caelo                    | Mometasone furoate, micronized | 15189806         | 1       |
| Caelo                    | Mometasone furoate, micronized | 15279004         | 2       |
| Caelo                    | Mometasone furoate, micronized | 15189809         | 1       |
| Caesar u Loretz          | Mometasone furoate, micronized | 15279004         | 2       |
| Fagron                   | Mometasone furoate, micronized | 15B11-B03        | 2       |
| Fagron                   | Mometasone furoate, micronized | 15B11-B03-304120 | 5       |
| Fagron                   | Mometasone furoate, micronized | 15B11-B03-304121 | 7       |
| Caelo                    | Mometasone furoate, micronized | 15B11-B03-304121 | 2       |
| Fagron                   | Mometasone furoate, micronized | 15B11B03304121   | 1       |
| Fagron                   | Mometasone furoate, micronized | 15B11B03304122   | 2       |
| Fagron                   | Mometasone furoate, micronized | 15B11-B03-304122 | 4       |
| Caelo                    | Mometasone furoate, micronized | 15B11B03304122   | 1       |
| Fagron                   | Mometasone furoate, micronized | 15B11-B03-304123 | 11      |
| Fagron                   | Mometasone furoate, micronized | 15B11-B03-304124 | 2       |
| Fagron                   | Mometasone furoate, micronized | 15B11-B03-308276 | 1       |
| Fagron                   | Mometasone furoate, micronized | 15b11-b03-304124 | 1       |
| Euro OTC                 | Mometasone furoate, micronized | 15B11-B03-308860 | 1       |
| Fagron                   | Mometasone furoate, micronized | 15B11-B03-308860 | 2       |
| Fagron                   | Mometasone furoate, micronized | 15G08-B11        | 2       |
| Fagron                   | Mometasone furoate, micronized | 15B11B03308860   | 1       |
| Fagron                   | Mometasone furoate, micronized | 15G08-B11-0002   | 1       |
| Fagron                   | Mometasone furoate, micronized | 15G08-B11-310864 | 5       |

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| Supplier                   | Substance                      | Batch            | Spectra |
|----------------------------|--------------------------------|------------------|---------|
| Caelo                      | Mometasone furoate, micronized | 15G08-B11-310864 | 1       |
| Caelo                      | Mometasone furoate, micronized | 15G08-B11-310865 | 1       |
| Fagron                     | Mometasone furoate, micronized | 15G08-B11-312233 | 4       |
| Fagron                     | Mometasone furoate, micronized | 15G08-B11-317182 | 6       |
| Caelo                      | Mometasone furoate, micronized | 15G08-B11-317182 | 1       |
| Euro OTC                   | Mometasone furoate, micronized | 15G08-B11-317182 | 1       |
| Fagron                     | Mometasone furoate, micronized | 15G08-B11-322737 | 3       |
| Fagron                     | Mometasone furoate, micronized | 15G08B11322738   | 1       |
| Fagron                     | Mometasone furoate, micronized | 15G08-B11-322738 | 2       |
| Fagron                     | Mometasone furoate, micronized | 15I11-B02-314479 | 4       |
| Fagron                     | Mometasone furoate, micronized | 15G-B11-310864   | 1       |
| Caelo                      | Mometasone furoate, micronized | 16028601         | 1       |
| Fagron                     | Mometasone furoate, micronized | 16/24-B11-332122 | 1       |
| Fagron                     | Mometasone furoate, micronized | 15J11-B02-315705 | 1       |
| Caelo                      | Mometasone furoate, micronized | 1602809          | 1       |
| Caesar&lorenz,AHC,08.08... | Mometasone furoate, micronized |                  | 1       |
| Caelo                      | Mometasone furoate, micronized | 16028602         | 4       |
| caesar&Loretz GmbH,Phön... | Mometasone furoate, micronized | 16028604         | 1       |
| Caelo                      | Mometasone furoate, micronized | 16028606         | 3       |
| Caelo                      | Mometasone furoate, micronized | 16028605         | 1       |
| Caelo                      | Mometasone furoate, micronized | 16028604         | 1       |
| Caelo                      | Mometasone furoate, micronized | 16028607         | 4       |
| Caelo                      | Mometasone furoate, micronized | 16028609         | 2       |
| Euro OTC                   | Mometasone furoate, micronized | 160602101        | 1       |
| Caelo                      | Mometasone furoate, micronized | 16028614         | 1       |
| Alte Apotheke              | Mometasone furoate, micronized | 1606021-01       | 1       |
| Euro OTC                   | Mometasone furoate, micronized | 1606021-01       | 2       |
| Euro OTC                   | Mometasone furoate, micronized | 1610009-01       | 2       |
| Caelo                      | Mometasone furoate, micronized | 16181704         | 4       |
| Gehe                       | Mometasone furoate, micronized | 16353201         | 1       |
| Caelo                      | Mometasone furoate, micronized | 16353206         | 1       |
| Caelo                      | Mometasone furoate, micronized | 16181715         | 2       |
| Fagron                     | Mometasone furoate, micronized | 16A20-B06        | 1       |
| Fagron                     | Mometasone furoate, micronized | 16724-B11-332112 | 1       |
| Fagron                     | Mometasone furoate, micronized | 16A20-B06-319748 | 2       |
| Fagron                     | Mometasone furoate, micronized | 16A20-B06-319749 | 5       |
| Fagron                     | Mometasone furoate, micronized | 16A20-B06319749  | 1       |
| Fagron                     | Mometasone furoate, micronized | 16A20-B06-322739 | 3       |
| Caelo                      | Mometasone furoate, micronized | 16A20-B06-319749 | 1       |
| Caelo                      | Mometasone furoate, micronized | 16C24B03324852   | 2       |
| Fagron                     | Mometasone furoate, micronized | 16C24-B03        | 2       |
| Fagron                     | Mometasone furoate, micronized | 16C24B03         | 1       |
| Fagron                     | Mometasone furoate, micronized | 16C24-B03-324852 | 1       |
| Fagron                     | Mometasone furoate, micronized | 16C24-B03-327346 | 2       |
| Phönix                     | Mometasone furoate, micronized | 16c24-b03-327346 | 1       |
| Fagron                     | Mometasone furoate, micronized | 16C24-B03-327372 | 3       |
| Fagron                     | Mometasone furoate, micronized | 16C24-B03-328272 | 1       |
| Fagron                     | Mometasone furoate, micronized | 16j24-b11-329817 | 1       |
| Fagron                     | Mometasone furoate, micronized | 16J24-B11-329817 | 2       |
| Caelo                      | Mometasone furoate, micronized | 16J24-B11-332112 | 1       |
| Fagron                     | Mometasone furoate, micronized | 16C24-b03-327372 | 1       |
| Fagron                     | Mometasone furoate, micronized | 1814E3640        | 1       |
| Fagron                     | Mometasone furoate, micronized | 16J24-B11-330978 | 2       |
| Fagron                     | Mometasone furoate, micronized | 1716I-07010      | 1       |
| Caelo                      | Mometasone furoate, micronized | 2/AKD2           | 1       |
| Caelo                      | Mometasone furoate, micronized | 200315A          | 1       |
| Fagron                     | Mometasone furoate, micronized | 2114M3640        | 1       |
| Fagron                     | Mometasone furoate, micronized | 2215I-07030      | 1       |
| Caelo                      | Mometasone furoate, micronized | 3/AKD11          | 1       |
| Fagron                     | Mometasone furoate, micronized | NS1513M          | 1       |

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| Supplier                   | Substance                      | Batch            | Spectra |
|----------------------------|--------------------------------|------------------|---------|
| Audor Pharma               | Mometasone furoate, micronized | APMOM010/0116M   | 2       |
| Caelo                      | Mometasone furoate, micronized | N01352M          | 1       |
| Fagron                     | Mometasone furoate, micronized | MOM008/0915      | 1       |
| Euro OTC                   | Mometasone furoate, micronized | 5991             | 1       |
| Fagron                     | Mometasone furoate, micronized | 3313A-07030      | 1       |
| Fagron                     | Mometasone furoate, micronized | NT1568M          | 4       |
| Synthexim/Phoenix          | Mometasone furoate, micronized | NT1568M          | 1       |
| Caelo                      | Mometasone furoate, micronized | NU0698M          | 1       |
| Fagron                     | Mometasone furoate, micronized | NU0698M          | 1       |
| Fagron                     | Mometasone furoate, micronized | NU2504M          | 2       |
| Caelo                      | Mometasone furoate, micronized | NV1000M          | 1       |
| Fagron                     | Mometasone furoate, micronized | 10G27-N05        | 1       |
| Fagron                     | Mometasone furoate, micronized | 11F08-N03        | 2       |
| v.d.l                      | Mometasone furoate, micronized | 11h10-n04        | 1       |
| Fagron                     | Mometasone furoate, micronized | 11H10-N01        | 3       |
| Caesar & Loretz GmbH, 4... | Mometasone furoate, micronized | 11H10-N04        | 1       |
| Phönix, 14.10.2013         | Mometasone furoate, micronized | 12351207         | 1       |
| Caesar & Loretz GmbH, 4... | Mometasone furoate, micronized | 12B22-N01        | 1       |
| Caelo                      | Mometasone furoate, micronized | 12035607         | 2       |
| Fagron                     | Mometasone furoate, micronized | 10C29-N10        | 1       |
| Caelo                      | Mometasone furoate, micronized | 12339604         | 1       |
| Caelo                      | Mometasone furoate, micronized | 12351203         | 1       |
| Fagron                     | Mometasone furoate, micronized | 13/23-N02        | 1       |
| Caelo                      | Mometasone furoate, micronized | 1235210          | 1       |
| Euro OTC                   | Mometasone furoate, micronized | 1307037-01       | 1       |
| Fagron                     | Mometasone furoate, micronized | 13D08N06         | 1       |
| Phönix                     | Mometasone furoate, micronized | 13D08-N06        | 1       |
| FARGON                     | Mometasone furoate, micronized | 13d08-n06        | 1       |
| Fagron                     | Mometasone furoate, micronized | 13F17-N01        | 9       |
| Fagron                     | Mometasone furoate, micronized | 13f17-n01        | 1       |
| Fagron                     | Mometasone furoate, micronized | 13F27-N02        | 8       |
| Fagron                     | Mometasone furoate, micronized | 13F27-N02        | 1       |
| Fagron                     | Mometasone furoate, micronized | 13j23n02         | 1       |
| Alliance Health 27.01.2... | Mometasone furoate, micronized | 13J23-N02        | 1       |
| Caelo                      | Mometasone furoate, micronized | 14281101         | 2       |
| Phoenix                    | Mometasone furoate, micronized | 14C07-B05-291268 | 1       |
| Caelo                      | Mometasone furoate, micronized | 18102013B        | 1       |
| Caelo                      | Mometasone furoate, micronized | 240913a          | 1       |
| Caelo                      | Mometasone furoate, micronized |                  | 2       |
| Fagron                     | Mometasone furoate, micronized | 10805-N12        | 1       |
| Fagron                     | Mometasone furoate, micronized | 11C02-N03        | 4       |
| Fagron                     | Mometasone furoate, micronized | 11h10-n04        | 1       |
| Kehr                       | Mometasone furoate, micronized | 12/29-N03        | 1       |
| Caelo                      | Mometasone furoate, micronized | 12035601         | 2       |
| Caesar & Loretz GmbH       | Mometasone furoate, micronized | 12035601         | 1       |
| Fagron                     | Mometasone furoate, micronized | 12/29-No3        | 1       |
| Euro OTC                   | Mometasone furoate, micronized | 1203024-02       | 1       |
| Caelo                      | Mometasone furoate, micronized | 12035608         | 3       |
| Caelo                      | Mometasone furoate, micronized | 12351201         | 1       |
| Caelo                      | Mometasone furoate, micronized | 12351207         | 1       |
| Caelo                      | Mometasone furoate, micronized | 12351210         | 1       |
| Fagron                     | Mometasone furoate, micronized | 12B22-N01        | 4       |
| Fagron                     | Mometasone furoate, micronized | 12B22-N04        | 1       |
| Caelo                      | Mometasone furoate, micronized | 12E02-N11        | 1       |
| Fagron                     | Mometasone furoate, micronized | 12e02-n11        | 1       |
| Fagron                     | Mometasone furoate, micronized | 12E02-N11        | 4       |
| Fagron                     | Mometasone furoate, micronized | 12H09-N02        | 11      |
| Anzag                      | Mometasone furoate, micronized | 12H09-N02        | 1       |
| Fagron                     | Mometasone furoate, micronized | 12I29-N03        | 1       |
| Fagron                     | Mometasone furoate, micronized | 12J29-N03        | 9       |

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| Supplier    | Substance                      | Batch            | Spectra |
|-------------|--------------------------------|------------------|---------|
| Anzag       | Mometasone furoate, micronized | 12J29N03         | 1       |
| Caelo       | Mometasone furoate, micronized | 1304011-01       | 1       |
| Caelo       | Mometasone furoate, micronized | 13D08-N06        | 1       |
| Anzag       | Mometasone furoate, micronized | 13D08-N06        | 1       |
| Gehe        | Mometasone furoate, micronized | 13D08-N06        | 1       |
| Fagron      | Mometasone furoate, micronized | 13F17-N01        | 1       |
| Caelo       | Mometasone furoate, micronized | 13F27-N02        | 2       |
| Fagron      | Mometasone furoate, micronized | 13F7-N01         | 1       |
| Fagron      | Mometasone furoate, micronized | 13H13-N04        | 1       |
| Caelo       | Mometasone furoate, micronized | 14E20-B04        | 1       |
| Phönix      | Mometasone furoate, micronized | 15b11-b03-30412  | 1       |
| Fagron      | Mometasone furoate, micronized | NS0420M          | 2       |
| Caelo       | Mometasone furoate, micronized | NT1568M          | 1       |
| Fagron      | Mometasone furoate, micronized | 11H10-N04        | 1       |
| Caeo/Noweda | Mometasone furoate, micronized | 15279003         | 1       |
| Fargon      | Mometasone furoate, micronized | 14h06-b07-298481 | 1       |
| Fagron      | Mometasone furoate, micronized | 15b11-b03-308276 | 1       |
| Herbasinica | Mometasone furoate, micronized | 12035602         | 1       |
| Caelo       | Mometasone furoate, micronized | 12035605         | 1       |
| Fagron      | Mometasone furoate, micronized | 2714U-07030      | 1       |
| Fagron      | Mometasone furoate, micronized | 12J29-N01        | 1       |
| Holdermann  | Mometasone furoate, micronized | 13D08-N06        | 1       |
| Gehe        | Mometasone furoate, micronized | 13H13-N04        | 2       |
| Holdermann  | Mometasone furoate, micronized | 14C07-B05-29126  | 1       |
| Fagron      | Mometasone furoate, micronized | 11k28-n09        | 1       |
| Caelo       | Mometasone furoate, micronized | 701834-0002      | 1       |
| Fargon      | Mometasone furoate, micronized | 13H13-N04        | 1       |

- 69 103 spectra from 414 *Apo-Ident* customers from a total of 23 602 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Mometasone furoate, micronized* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Mometasone furoate, micronized* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 330           | 0              | 71 056        |
| <b>Type B</b> | 0              | 349           | 70             | 146 310       |
| <b>Type C</b> | 0              | 367           | 163            | 69 103        |

The substance/substance group *Mometasone furoate, micronized* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.1818 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 83.2936 % (> 82.5776 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 69.2453 % (> 68.6792 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20850     | 22433               | 4.20                         | 69.54                           |
| 21602     | 22433               | 4.78                         | 78.11                           |
| 22238     | 22238               | 0.00                         | 72.79                           |
| 22433     | 22433               | 0.00                         | 72.24                           |
| 22887     | 22433               | 3.13                         | 68.96                           |
| 23136     | 23136               | 0.00                         | 68.80                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

IdentModul 1.3-2018-01

Validated substance/substance group **Monostereates**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20691-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

## Relevant substance names

Monostereates; Glycerinum monostearinicum 40-55%; Glycerinum monostearinicum 60; Glycerinum monostearinicum emulsificantes; Glycerol monostearate 40-55%; Glycerol monostearate 60; Glycerol monostearate, self-emulsifying; Glyceroli monostearates 40-55%; Glyceroli monostearates 60; Glyceroli monostearates emulsificantes; Sorbitan stearate; Sorbitani steareas; Sorbitanum monostearinicum

## Special notes

When selecting the *Monostereates* substance/substance group, the following information is displayed to the user:

*no information*

## Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

## Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

## Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Monostereates*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Glycerol monoste... | 12105705 | 20691     | 80      | 20120424    |
| Caelo    | Glycerol monoste... | 12210401 | 20751     | 80      | 1407214     |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Caelo    | Glycerol monoste... | 12210401         | 20783     | 40      | 20120726           |
| Caelo    | Sorbitan stearate   | 12274801         | 20828     | 40      | 20120924           |
| Caelo    | Glycerol monoste... | 12105720         | 20867     | 40      | 20120424           |
| Caelo    | Glycerol monoste... | 13109304         | 21093     | 40      | 1407633            |
| Caelo    | Glycerol monoste... | 13232604         | 21437     | 40      | 1504599            |
| Caelo    | Glycerol monoste... | 14099903         | 21446     | 40      | AR-15-FG-000732-02 |
| Caelo    | Glycerol monoste... | 14240607         | 21576     | 40      | 1412120            |
| Caelo    | Glycerol monoste... | 14240607         | 21585     | 40      | 20140815           |
| Fagron   | Sorbitan stearate   | 14J07-B02-299399 | 21885     | 40      | AR-16-FG-004368-01 |
| Caelo    | Glycerol monoste... | 15286302         | 21982     | 40      | 20150911           |
| Caelo    | Glycerol monoste... | 14308310         | 21993     | 40      | 20150109           |
| Fagron   | Glycerol monoste... | 15E13-B03-305532 | 22277     | 40      | 20150703           |
| Caelo    | Glycerol monoste... | 15286302         | 22320     | 40      | AR-16-FG-009226-01 |
| Caelo    | Glycerol monoste... | 154450           | 22464     | 40      | 20160225*          |
| Caelo    | Glycerol monoste... | 161646           | 22623     | 40      | 20160727*          |
| Caelo    | Glycerol monoste... | 16030301         | 22667     | 40      | 20160204           |
| Caelo    | Glycerol monoste... | 162338           | 22743     | 40      | 20160822*          |
| Caelo    | Sorbitan stearate   | 162352           | 22764     | 40      | 20160826*          |
| Caelo    | Glycerol monoste... | 16233804         | 23188     | 40      | 10052              |
| Caelo    | Sorbitan stearate   | 17030805         | 23706     | 40      | 20170210           |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 960 spectra of 22 reference samples from the substance/substance group *Monostereates*. These samples are listed above in the [calibration samples](#) section.
- 70 426 spectra from a total of 1533 batches from further 371 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 1121 spectra of 29 reference samples from the substance/substance group *Monostereates*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.



| Supplier | Substance                       | Batch            | Sample ID          | Spectra |
|----------|---------------------------------|------------------|--------------------|---------|
| Fagron   | Glycerol monostearate 40-55%    | 8J14-M04         | 20039              | 31      |
| Caelo    | Glycerol monostearate 60        | 10097203         | 20175              | 40      |
| Caelo    | Glycerol monostearate, self-... | 10080113         | 20286              | 30      |
| Caelo    | Sorbitan stearate               | 11145401         | 20351              | 40      |
| Caelo    | Glycerol monostearate 60        | 1127201902       | 20576              | 40      |
| Caelo    | Glycerol monostearate 60        | 11272902         | 20608              | 40      |
| Caelo    | Glycerol monostearate, self-... | 11079309         | 20621              | 80      |
| Caelo    | Glycerol monostearate 60        | 11272902         | 20677              | 80      |
| Fagron   | Sorbitan stearate               | 11I26-N09        | 20736              | 40      |
| Fagron   | Glycerol monostearate, self-... | 11I15-N09        | 20746              | 80      |
| Fagron   | Glycerol monostearate, self-... | 12B14-N10        | 20786              | 40      |
| Caelo    | Glycerol monostearate 60        | 13232604         | 21437 <sup>†</sup> | 20      |
| Caelo    | Glycerol monostearate 40-55%    | 14099903         | 21446 <sup>†</sup> | 20      |
| Fagron   | Glycerol monostearate 40-55%    | 14C12-B40-292622 | 21545              | 60      |
| Caelo    | Glycerol monostearate, self-... | 14240607         | 21576 <sup>†</sup> | 20      |
| Caelo    | Glycerol monostearate, self-... | 14240607         | 21585 <sup>†</sup> | 20      |
| Fagron   | Sorbitan stearate               | 14J07-B02-299399 | 21885 <sup>†</sup> | 20      |
| Caelo    | Glycerol monostearate 60        | 15286302         | 21982 <sup>†</sup> | 20      |
| Caelo    | Glycerol monostearate, self-... | 14308310         | 21993 <sup>†</sup> | 20      |
| Fagron   | Glycerol monostearate 40-55%    | 15E13-B03-305532 | 22277 <sup>†</sup> | 20      |
| Caelo    | Glycerol monostearate, self-... | 14308310         | 22278              | 60      |
| Caelo    | Glycerol monostearate 60        | 15286302         | 22320 <sup>†</sup> | 20      |
| Caelo    | Glycerol monostearate, self-... | 14308310         | 22341              | 60      |
| Caelo    | Glycerol monostearate 40-55%    | 154450           | 22464 <sup>†</sup> | 20      |
| Caelo    | Glycerol monostearate 60        | 162338           | 22646              | 40      |
| Caelo    | Glycerol monostearate 60        | 162338           | 22741              | 40      |
| Caelo    | Glycerol monostearate 60        | 162338           | 22742              | 40      |
| Caelo    | Glycerol monostearate 60        | 162338           | 22744              | 40      |
| Caelo    | Sorbitan stearate               | 171781           | 23622              | 40      |

- 145 608 spectra from a total of 3173 batches from further 859 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 137 spectra from 78 *Apo-Ident* customers from 70 batches from the substance/substance group *Monostereates*.

| Supplier | Substance                       | Batch     | Spectra |
|----------|---------------------------------|-----------|---------|
| Caelo    | Glycerol monostearate 60        | 13109304  | 9       |
| Caelo    | Glycerol monostearate, self-... | 13109402  | 1       |
| Caelo    | Glycerol monostearate, self-... | 13109405  | 3       |
| Caelo    | Glycerol monostearate, self-... | 13109409  | 2       |
| Caelo    | Glycerol monostearate, self-... | 13109410  | 1       |
| Caelo    | Glycerol monostearate 40-55%    | 131156602 | 1       |
| Caelo    | Glycerol monostearate 40-55%    | 13221308  | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier               | Substance                       | Batch            | Spectra |
|------------------------|---------------------------------|------------------|---------|
| Caelo                  | Glycerol monostearate 60        | 14012002         | 4       |
| Caelo                  | Glycerol monostearate 40-55%    | 14169701         | 1       |
| Caelo                  | Glycerol monostearate 40-55%    | 14169710         | 1       |
| Caelo                  | Glycerol monostearate 40-55%    | 14169717         | 2       |
| Caelo                  | Glycerol monostearate, self-... | 1420607          | 1       |
| Gehe                   | Glycerol monostearate, self-... | 14240605         | 2       |
| Caelo                  | Glycerol monostearate, self-... | 14240607         | 1       |
| Caelo                  | Glycerol monostearate, self-... | 14240611         | 1       |
| Caelo                  | Glycerol monostearate, self-... | 14308310         | 3       |
| Caelo                  | Glycerol monostearate 60        | 15009203         | 6       |
| Caelo                  | Glycerol monostearate 40-55%    | 15280903         | 2       |
| Caelo                  | Glycerol monostearate 40-55%    | 15445007         | 1       |
| Caelo                  | Glycerol monostearate, self-... | 16030301         | 2       |
| Noweda                 | Glycerol monostearate, self-... | 11079301         | 1       |
| Caelo                  | Glycerol monostearate, self-... | 16030304         | 1       |
| Caelo                  | Glycerol monostearate 40-55%    | 12105729         | 1       |
| Caelo                  | Glycerol monostearate, self-... | 11079308         | 1       |
| Fagron                 | Glycerol monostearate 40-55%    | 12K05-N06        | 2       |
| Caesar/Noweda          | Glycerol monostearate 60        | 13109304         | 1       |
| Caesar u Loretz        | Glycerol monostearate 60        | 13109304         | 1       |
| Caelo                  | Glycerol monostearate 40-55%    | 13156601         | 3       |
| Spangropharm           | Glycerol monostearate 40-55%    | 80402468         | 1       |
| Anzag                  | Glycerol monostearate 60        | 12180502         | 1       |
| Caesar/Noweda          | Glycerol monostearate 40-55%    | 13221311         | 2       |
| Audor Pharma           | Glycerol monostearate 60        | 13232604         | 1       |
| Caelo                  | Glycerol monostearate 60        | 13232604         | 1       |
| Caesar u Loretz        | Glycerol monostearate 60        | 14012002         | 1       |
| Noweda                 | Glycerol monostearate 60        | 15009203         | 1       |
| Caesar & Loretz/Noweda | Glycerol monostearate 60        | 15009203         | 1       |
| Caelo                  | Glycerol monostearate 60        | 15286302         | 1       |
| Fagron                 | Glycerol monostearate 40-55%    | 15E13-B03        | 1       |
| Euro OTC               | Glycerol monostearate 60        | 16233804         | 1       |
| Fagron                 | Glycerol monostearate 40-55%    | 7G19-N09         | 1       |
| Fagron                 | Glycerol monostearate 40-55%    | 12A27-N11        | 1       |
| Caelo                  | Glycerol monostearate 60        | 13018201         | 3       |
| Caelo                  | Glycerol monostearate 60        | 1301821          | 1       |
| Phonix                 | Glycerol monostearate 60        | 13109304         | 1       |
| Caelo                  | Glycerol monostearate 40-55%    | 13221303         | 2       |
| Fagron                 | Glycerol monostearate 40-55%    | CG10980003       | 1       |
| Caelo                  | Sorbitan stearate               | 13209409         | 1       |
| Caelo                  | Sorbitan stearate               | 13209417         | 3       |
| Caelo                  | Sorbitan stearate               | 13209418         | 2       |
| Caelo                  | Sorbitan stearate               | 13209419         | 3       |
| Caelo                  | Sorbitan stearate               | 14038504         | 1       |
| Caelo                  | Sorbitan stearate               | 14038510         | 1       |
| Caelo                  | Sorbitan stearate               | 14038511         | 2       |
| Caelo                  | Sorbitan stearate               | 14218803         | 4       |
| Caelo                  | Sorbitan stearate               | 14218804         | 1       |
| Caelo                  | Sorbitan stearate               | 14218808         | 3       |
| Ichthyol/Phoenix       | Sorbitan stearate               | 14372803         | 1       |
| Fagron                 | Sorbitan stearate               | 14J07-B02-299399 | 1       |
| Caelo                  | Sorbitan stearate               | 14372803         | 1       |
| Caelo                  | Sorbitan stearate               | 15300302         | 5       |
| Caelo                  | Sorbitan stearate               | 15300308         | 2       |
| Caelo                  | Sorbitan stearate               | 15415202         | 4       |
| Caelo                  | Sorbitan stearate               | 17030805         | 1       |
| Caelo                  | Sorbitan stearate               | 26031507         | 1       |
| Caelo                  | Sorbitan stearate               | 11145411         | 1       |
| Großhandel             | Sorbitan stearate               | 12274801         | 1       |
| Caelo                  | Sorbitan stearate               | 12274813         | 2       |

*continued on the next page*



continued from previous page

| Supplier        | Substance                       | Batch     | Spectra |
|-----------------|---------------------------------|-----------|---------|
| Fagron          | Sorbitan stearate               | 12E30-N14 | 1       |
| Caelo           | Sorbitan stearate               | 12h23-n05 | 1       |
| Caelo           | Sorbitan stearate               | 13209410  | 1       |
| Phonix          | Sorbitan stearate               | 13209418  | 1       |
| Caelo           | Sorbitan stearate               | 13B19-N01 | 1       |
| Fagron          | Sorbitan stearate               | 13B19-N01 | 2       |
| Gehe 16.04.2013 | Sorbitan stearate               | 13B19-N01 | 1       |
| Fagron          | Sorbitan stearate               | 13D10N10  | 1       |
| Fagron          | Sorbitan stearate               | 13D10-N10 | 1       |
| Caelo           | Sorbitan stearate               | 13209409  | 2       |
| Fagron          | Sorbitan stearate               | 5052      | 1       |
| Caelo           | Sorbitan stearate               | 12085011  | 1       |
| Caelo           | Sorbitan stearate               | 12274801  | 1       |
| Caelo           | Sorbitan stearate               | 12274807  | 1       |
| Nachprüfung     | Sorbitan stearate               |           | 1       |
| Caelo           | Glycerol monostearate, self-... | 13109404  | 1       |

- 69 496 spectra from 414 *Apo-Ident* customers from a total of 23 733 batches from a further 693 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Monostereates* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Monostereates* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 960           | 0              | 70 426        |
| <b>Type B</b> | 0              | 859           | 262            | 145 608       |
| <b>Type C</b> | 0              | 129           | 8              | 69 496        |

The substance/substance group *Monostereates* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 99.3750 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 76.6280 % (> 76.3604 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 94.1606 % (> 91.9708 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20691     | 21446               | 11.40                        | 42.01                           |
| 20751     | 20751               | 0.00                         | 33.46                           |
| 20783     | 20751               | 2.60                         | 33.34                           |
| 20828     | 22764               | 18.32                        | 46.27                           |
| 20867     | 21446               | 17.00                        | 40.03                           |
| 21093     | 21093               | 0.00                         | 25.54                           |
| 21437     | 21437               | 0.00                         | 33.67                           |
| 21446     | 21446               | 0.00                         | 43.53                           |
| 21576     | 21576               | 0.00                         | 29.67                           |
| 21585     | 21576               | 1.59                         | 30.62                           |
| 21885     | 21885               | 0.00                         | 19.73                           |
| 21982     | 22320               | 3.05                         | 25.83                           |
| 21993     | 20751               | 9.97                         | 31.93                           |
| 22277     | 21446               | 19.76                        | 39.33                           |
| 22320     | 22320               | 0.00                         | 26.27                           |
| 22464     | 22464               | 0.00                         | 48.64                           |
| 22623     | 22623               | 0.00                         | 19.83                           |
| 22667     | 20751               | 7.98                         | 31.48                           |
| 22743     | 22743               | 0.00                         | 23.52                           |
| 22764     | 22764               | 0.00                         | 39.93                           |
| 23188     | 23188               | 0.00                         | 28.43                           |
| 23706     | 22764               | 2.37                         | 40.46                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Mupirocin calcium**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20781-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Mupirocin calcium; Calcii mupirocini; Mupirocinum calcii

### Special notes

When selecting the *Mupirocin calcium* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Mupirocin calcium*:

| Supplier | Substance         | Batch     | Sample ID | Spectra | Certificate |
|----------|-------------------|-----------|-----------|---------|-------------|
| Fagron   | Mupirocin calcium | 12E02-N07 | 20781     | 40      | 1401556     |
| Caelo    | Mupirocin calcium | 14276602  | 21745     | 40      | 20141103    |
| Caelo    | Mupirocin calcium | 161184    | 22454     | 40      | 20160504*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Mupirocin calcium*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 3 reference samples from the substance/substance group *Mupirocin calcium*.

| Supplier | Substance         | Batch            | Sample ID          | Spectra |
|----------|-------------------|------------------|--------------------|---------|
| Caelo    | Mupirocin calcium | 14276602         | 21745 <sup>†</sup> | 20      |
| Caelo    | Mupirocin calcium | 161184           | 22454 <sup>†</sup> | 20      |
| Fagron   | Mupirocin calcium | 15H13-B01-316111 | 23213              | 40      |

- 146 649 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 4 spectra from 4 *Apo-Ident* customers from 4 batches from the substance/substance group *Mupirocin calcium*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance         | Batch            | Spectra |
|----------|-------------------|------------------|---------|
| Fagron   | Mupirocin calcium | 14B03-B30-299165 | 1       |
| Fagron   | Mupirocin calcium | 15H13-B01        | 1       |
| Caelo    | Mupirocin calcium | 83200301013      | 1       |
| Fagron   | Mupirocin calcium | 14B03-B30-297291 | 1       |

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Mupirocin calcium* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Mupirocin calcium* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 44            | 36             | 146 649       |
| <b>Type C</b> | 0              | 2             | 2              | 69 629        |

The substance/substance group *Mupirocin calcium* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 55.0000 % (> 51.2500 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20781     | 20781               | 0.00                         | 50.99                           |
| 21745     | 22454               | 7.84                         | 51.94                           |
| 22454     | 22454               | 0.00                         | 51.52                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Naloxone hydrochloride dihydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20957-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Naloxone hydrochloride dihydrate; Naloxoni hydrochloridum dihydricum

### Special notes

When selecting the *Naloxone hydrochloride dihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Naloxone hydrochloride dihydrate*:

| Supplier | Substance           | Batch         | Sample ID | Spectra | Certificate |
|----------|---------------------|---------------|-----------|---------|-------------|
| Fagron   | Naloxone hydroch... | 13D22-N07     | 20957     | 40      | 1402059     |
| Fagron   | Naloxone hydroch... | 13L12-B03     | 21271     | 40      | 20140113    |
| Audor    | Naloxone hydroch... | AP13501078IIN | 22811     | 40      | 20160429    |
| Caelo    | Naloxone hydroch... | 163577        | 23039     | 40      | 20170306*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Naloxone hydrochloride dihydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 40 spectra of 1 reference samples from the substance/substance group *Naloxone hydrochloride dihydrate*.

| Supplier | Substance                       | Batch    | Sample ID | Spectra |
|----------|---------------------------------|----------|-----------|---------|
| Caelo    | Naloxone hydrochloride dihyd... | 15322517 | 22828     | 40      |

- 146 689 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 25 spectra from 8 *Apo-Ident* customers from 17 batches from the substance/substance group *Naloxone hydrochloride dihydrate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.



| Supplier     | Substance                       | Batch            | Spectra |
|--------------|---------------------------------|------------------|---------|
| Fagron       | Naloxone hydrochloride dihyd... | 12G19-N02        | 1       |
| Fagron       | Naloxone hydrochloride dihyd... | 13D22-N07        | 1       |
| Phönix       | Naloxone hydrochloride dihyd... | 13L12-B03-289511 | 1       |
| Fagron       | Naloxone hydrochloride dihyd... | 14F20-B02-296077 | 2       |
| Caelo        | Naloxone hydrochloride dihyd... | 15322521         | 1       |
| Fagron       | Naloxone hydrochloride dihyd... | 15B06-B02-304421 | 1       |
| Fagron       | Naloxone hydrochloride dihyd... | 15E28-B01-308324 | 4       |
| Fagron       | Naloxone hydrochloride dihyd... | 15H04-B09-314068 | 1       |
| Caelo        | Naloxone hydrochloride dihyd... | 17044101         | 1       |
| Fagron       | Naloxone hydrochloride dihyd... | 15K11-B05        | 1       |
| Audor Pharma | Naloxone hydrochloride dihyd... | AP13501078N      | 1       |
| Fagron       | Naloxone hydrochloride dihyd... | 14F20-B02        | 1       |
| Fagron       | Naloxone hydrochloride dihyd... | 14A28-B33-296076 | 1       |
| Fagron       | Naloxone hydrochloride dihyd... | 15B06-B02-304420 | 1       |
| Fagron       | Naloxone hydrochloride dihyd... | 15H04-B09        | 3       |
| Fagron       | Naloxone hydrochloride dihyd... | 13L12-B03        | 3       |
| Fagron       | Naloxone hydrochloride dihyd... | 15K11-B05-319571 | 1       |

- 69 608 spectra from 414 *Apo-Ident* customers from a total of 23 787 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Naloxone hydrochloride dihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Naloxone hydrochloride dihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 40            | 0              | 146 689       |
| <b>Type C</b> | 0              | 21            | 4              | 69 600        |

The substance/substance group *Naloxone hydrochloride dihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 85.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | 84.0000 % (> 72.0000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20957     | 20957               | 0.00                         | 43.35                           |
| 21271     | 20957               | 5.24                         | 41.62                           |
| 22811     | 20957               | 13.67                        | 45.84                           |
| 23039     | 23039               | 0.00                         | 46.48                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Naphazoline hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20899-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Naphazoline hydrochloride; Naphazolini hydrochloridum; Naphazolinum hydrochloricum

### Special notes

When selecting the *Naphazoline hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Naphazoline hydrochloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------|-----------|---------|--------------------|
| Caelo    | Naphazoline hydr... | 12375211   | 20899     | 40      | 20130108           |
| Euro OTC | Naphazoline hydr... | 1407034-01 | 21623     | 40      | AR-15-FG-007847-01 |
| Euro OTC | Naphazoline hydr... | 1506015    | 21859     | 40      | 20150727*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Naphazoline hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 6 reference samples from the substance/substance group *Naphazoline hydrochloride*.

| Supplier | Substance                 | Batch      | Sample ID          | Spectra |
|----------|---------------------------|------------|--------------------|---------|
| Caelo    | Naphazoline hydrochloride | 12375211   | 21397              | 60      |
| Caelo    | Naphazoline hydrochloride | 12375211   | 21398              | 60      |
| Euro OTC | Naphazoline hydrochloride | 1407034-01 | 21623 <sup>†</sup> | 20      |
| Euro OTC | Naphazoline hydrochloride | 1506015    | 21859 <sup>†</sup> | 20      |
| Euro OTC | Naphazoline hydrochloride | 1607041    | 22753              | 40      |
| Euro OTC | Naphazoline hydrochloride | 1704005    | 23385              | 40      |

- 146 489 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 85 spectra from 66 *Apo-Ident* customers from 54 batches from the substance/substance group *Naphazoline hydrochloride*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier          | Substance                 | Batch              | Spectra |
|-------------------|---------------------------|--------------------|---------|
| Fagron            | Naphazoline hydrochloride | 588710001          | 2       |
| Euro OTC          | Naphazoline hydrochloride | 616620001          | 1       |
| Fagron            | Naphazoline hydrochloride | 60494000113K27-N04 | 1       |
| Caelo             | Naphazoline hydrochloride | 11081107           | 2       |
| Euro OTC          | Naphazoline hydrochloride | 1206037-02         | 4       |
| Caelo             | Naphazoline hydrochloride | 12375211           | 1       |
| Caelo             | Naphazoline hydrochloride | 1216203            | 1       |
| Fagron            | Naphazoline hydrochloride | 13/03-B03-295105   | 1       |
| Fagron            | Naphazoline hydrochloride | 13/03-B03-305291   | 1       |
| Caelo             | Naphazoline hydrochloride | 13372603           | 1       |
| Fagron            | Naphazoline hydrochloride | 13/03-B03305291    | 1       |
| Fagron            | Naphazoline hydrochloride | 13A07-N06          | 4       |
| Fagron            | Naphazoline hydrochloride | 13I03-B03          | 1       |
| Fagron            | Naphazoline hydrochloride | 13I03-B03-295105   | 2       |
| Fagron            | Naphazoline hydrochloride | 13I03-B03-305291   | 2       |
| Fagron            | Naphazoline hydrochloride | 13K27-N04          | 7       |
| Caelo             | Naphazoline hydrochloride | 13I03-B03-305291   | 1       |
| Fagron            | Naphazoline hydrochloride | 13k27-n04          | 1       |
| Fagron            | Naphazoline hydrochloride | 13I03-B03-295105   | 1       |
| Euro OTC          | Naphazoline hydrochloride | 14070034-01        | 1       |
| Euro OTC          | Naphazoline hydrochloride | 1407034-01         | 1       |
| Euro OTC          | Naphazoline hydrochloride | 1407034-02         | 1       |
| Euro OTC          | Naphazoline hydrochloride | 1506015-01         | 1       |
| Caelo             | Naphazoline hydrochloride | 15071404           | 1       |
| Euro OTC          | Naphazoline hydrochloride | 1506015-02         | 3       |
| Euro OTC          | Naphazoline hydrochloride | 150601502          | 1       |
| Caelo             | Naphazoline hydrochloride | 15223301           | 2       |
| Caelo             | Naphazoline hydrochloride | 1506015-2          | 1       |
| Fagron            | Naphazoline hydrochloride | 15J05-B05          | 1       |
| Fagron            | Naphazoline hydrochloride | 15J05-B05-322527   | 1       |
| Fagron            | Naphazoline hydrochloride | 15J05-B05-326850   | 2       |
| Fagron            | Naphazoline hydrochloride | 17C02-B05          | 1       |
| Phönix            | Naphazoline hydrochloride | 586550002          | 1       |
| Euro OTC          | Naphazoline hydrochloride | 1607041-01         | 1       |
| Caelo             | Naphazoline hydrochloride | 9285103            | 3       |
| Fagron            | Naphazoline hydrochloride | 4509E-01885        | 2       |
| Caelo             | Naphazoline hydrochloride | 11081112           | 1       |
| Fagron            | Naphazoline hydrochloride | 11/05-N02          | 1       |
| Anzag, 10.10.2012 | Naphazoline hydrochloride | 11081112           | 2       |
| Caleo /Herba      | Naphazoline hydrochloride | 9285103            | 1       |
| Euro OTC          | Naphazoline hydrochloride | 1103031-02         | 1       |
| Euro OTC          | Naphazoline hydrochloride | 113031-01          | 1       |
| Fagron            | Naphazoline hydrochloride | 11I05-N02          | 3       |
| Fagron            | Naphazoline hydrochloride | 11J13-N08          | 1       |
| Fagron            | Naphazoline hydrochloride | 11K25-N03          | 1       |
| Euro OTC          | Naphazoline hydrochloride | 1206037-01         | 1       |
| Caelo             | Naphazoline hydrochloride | 12176203           | 1       |
| Caelo             | Naphazoline hydrochloride | 1307020-02         | 1       |
| Fagron            | Naphazoline hydrochloride | 12K29-N01o256/310  | 1       |
| Fagron            | Naphazoline hydrochloride | 13C11-N07          | 3       |
| Fagron            | Naphazoline hydrochloride | 13C11N07           | 1       |
| Caelo             | Naphazoline hydrochloride | 15223303           | 1       |
| Caelo             | Naphazoline hydrochloride | 2275310            | 1       |
| Fagron            | Naphazoline hydrochloride | 4309I-01885        | 1       |
| Eurho/Phoenix     | Naphazoline hydrochloride | 4413I-01885        | 1       |
| Caelo             | Naphazoline hydrochloride | 12375203           | 1       |
| Caelo             | Naphazoline hydrochloride | 1206037            | 1       |

- 69 548 spectra from 414 *Apo-Ident* customers from a total of 23 747 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Naphazoline hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Naphazoline hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 120           | 0              | 71 266        |
| Type B | 0              | 240           | 0              | 146 489       |
| Type C | 0              | 82            | 3              | 69 548        |

The substance/substance group *Naphazoline hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| Type C | 100.0000 % (> 99.8813 %) | 96.4706 % (> 92.9412 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20899     | 21623               | 8.05                         | 40.73                           |
| 21623     | 21623               | 0.00                         | 38.53                           |
| 21859     | 21859               | 0.00                         | 37.71                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Naphazoline nitrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20501-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Naphazoline nitrate; Naphazolini nitras; Naphazolinum nitricum

### Special notes

When selecting the *Naphazoline nitrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Naphazoline nitrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Naphazoline nitr... | 12L10-N03        | 20846     | 40      | 20121217    |
| Fagron   | Naphazoline nitr... | 12J08-B40-287904 | 21808     | 40      | 20131129    |
| Euro OTC | Naphazoline nitr... | 1512033          | 22302     | 40      | 20160126*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Naphazoline nitrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 159 spectra of 5 reference samples from the substance/substance group *Naphazoline nitrate*.

| Supplier | Substance           | Batch            | Sample ID          | Spectra |
|----------|---------------------|------------------|--------------------|---------|
| Fagron   | Naphazoline nitrate | 11K21-N24        | 20501              | 39      |
| Fagron   | Naphazoline nitrate | 12J08-B40-287904 | 21808 <sup>†</sup> | 20      |
| Euro OTC | Naphazoline nitrate | 1512033          | 22302 <sup>†</sup> | 20      |
| Fagron   | Naphazoline nitrate | 16A14-B03-327343 | 23164              | 40      |
| Euro OTC | Naphazoline nitrate | 1512033-01       | 23275              | 40      |

- 146 570 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 9 spectra from 9 *Apo-Ident* customers from 8 batches from the substance/substance group *Naphazoline nitrate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier     | Substance           | Batch            | Spectra |
|--------------|---------------------|------------------|---------|
| Fagron       | Naphazoline nitrate | 12/21-N05        | 1       |
| Fagron       | Naphazoline nitrate | 12I21-N05        | 1       |
| Fagron       | Naphazoline nitrate | 12J08-B40        | 1       |
| Fagron       | Naphazoline nitrate | 12J08-B40-294166 | 1       |
| Fagron       | Naphazoline nitrate | 12j08-b40-303401 | 1       |
| Fagron       | Naphazoline nitrate | 16A14-B03-322534 | 1       |
| Fagron       | Naphazoline nitrate | 21021304         | 1       |
| Audor Pharma | Naphazoline nitrate | 12I21-N05        | 1       |
| Fagron       | Naphazoline nitrate | 12J08B40-294166  | 1       |

- 69 624 spectra from 414 *Apo-Ident* customers from a total of 23 793 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Naphazoline nitrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Naphazoline nitrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 159           | 0              | 146 570       |
| <b>Type C</b> | 0              | 9             | 0              | 69 624        |

The substance/substance group *Naphazoline nitrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.2264 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20846     | 22302               | 5.34                         | 54.11                           |
| 21808     | 22302               | 3.35                         | 51.32                           |
| 22302     | 22302               | 0.00                         | 46.49                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Naproxen**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22316-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Naproxen; Naproxenum

### Special notes

When selecting the *Naproxen* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Naproxen*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------|------------------|-----------|---------|--------------------|
| Fagron   | Naproxen  | 15F18-B03-309492 | 22316     | 30      | AR-16-FG-008486-02 |
| Fagron   | Naproxen  | 15F18-B03-315691 | 22327     | 30      | 20150703           |
| Fagron   | Naproxen  | 16B04-B09-326261 | 23105     | 40      | 20160229           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 100 spectra of 3 reference samples from the substance/substance group *Naproxen*. These samples are listed above in the [calibration samples](#) section.
- 71 286 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 54 spectra of 3 reference samples from the substance/substance group *Naproxen*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Fagron   | Naproxen  | 15F18-B03-309492 | 22316 <sup>†</sup> | 15      |
| Fagron   | Naproxen  | 15F18-B03-315691 | 22327 <sup>†</sup> | 15      |
| Fagron   | Naproxen  | 16B04-B09-321569 | not required       | 24      |

- 146 675 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Naproxen*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Naproxen* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Naproxen* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 100           | 0              | 71 286        |
| <b>Type B</b> | 0              | 54            | 0              | 146 675       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Naproxen* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 88.8889 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22316     | 22316               | 0.00                         | 39.04                           |
| 22327     | 22316               | 0.74                         | 38.66                           |
| 23105     | 22316               | 4.63                         | 38.21                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Neomycin sulfate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20544-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Neomycin sulfate; Neomycin sulphate; Neomycini sulfas; Neomycinum sulfuricum

### Special notes

When selecting the *Neomycin sulfate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Neomycin sulfate*:

| Supplier | Substance        | Batch            | Sample ID | Spectra | Certificate        |
|----------|------------------|------------------|-----------|---------|--------------------|
| Euro OTC | Neomycin sulfate | 1303033-03       | 21771     | 40      | AR-15-FG-016582-01 |
| Caelo    | Neomycin sulfate | 13062923         | 21814     | 40      | AR-15-FG-016581-01 |
| Fagron   | Neomycin sulfate | 14C27-B05-302516 | 21894     | 40      | 1604527            |
| Fagron   | Neomycin sulfate | 14C27-B05-302517 | 21961     | 40      | 20140418           |
| Caelo    | Neomycin sulfate | 13062923         | 22276     | 30      | 20130315           |
| Euro OTC | Neomycin sulfate | 1601046          | 22381     | 30      | 20160212*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 220 spectra of 6 reference samples from the substance/substance group *Neomycin sulfate*. These samples are listed above in the [calibration samples](#) section.
- 71 166 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 395 spectra of 12 reference samples from the substance/substance group *Neomycin sulfate*.

| Supplier | Substance        | Batch            | Sample ID          | Spectra |
|----------|------------------|------------------|--------------------|---------|
| Fagron   | Neomycin sulfate | 11C13-N04        | 20544              | 40      |
| Euro OTC | Neomycin sulfate | 1102043-02       | 20758              | 40      |
| Euro OTC | Neomycin sulfate | 1303033-03       | 21771 <sup>†</sup> | 20      |
| Caelo    | Neomycin sulfate | 13062923         | 21814 <sup>†</sup> | 20      |
| Fagron   | Neomycin sulfate | 14C27-B05-302516 | 21894 <sup>†</sup> | 20      |
| Fagron   | Neomycin sulfate | 14C27-B05-302517 | 21961 <sup>†</sup> | 20      |
| Caelo    | Neomycin sulfate | 13062923         | 22276 <sup>†</sup> | 15      |
| Euro OTC | Neomycin sulfate | 1601046          | 22381 <sup>†</sup> | 15      |
| Caelo    | Neomycin sulfate | 15237602         | 22389              | 40      |
| Fagron   | Neomycin sulfate | 14C27-B05-302516 | 21894SI            | 60      |
| Fagron   | Neomycin sulfate | 14C27-B05-302517 | 21961SI            | 60      |
| Caelo    | Neomycin sulfate | 13062923         | 22276SI            | 45      |

- 146 334 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 276 spectra from 137 *Apo-Ident* customers from 85 batches from the substance/substance group *Neomycin sulfate*.

| Supplier                   | Substance        | Batch            | Spectra |
|----------------------------|------------------|------------------|---------|
| Euro OTC                   | Neomycin sulfate | 1102043-02       | 12      |
| Caelo                      | Neomycin sulfate | 13062923         | 3       |
| VDL Nachliefer; 2.7.15;... | Neomycin sulfate | 1303033-03       | 2       |
| Euro/phönix                | Neomycin sulfate | 1502004-01       | 1       |
| Euro OTC                   | Neomycin sulfate | 1502004-01       | 14      |
| Caelo                      | Neomycin sulfate | 10157505         | 7       |
| Bombastus                  | Neomycin sulfate | 1601046-01       | 2       |
| Caelo                      | Neomycin sulfate | 9051402          | 1       |
| Caelo                      | Neomycin sulfate | 9105308          | 1       |
| Caelo                      | Neomycin sulfate | 12276410         | 2       |
| Noweda                     | Neomycin sulfate | 1102043-02       | 1       |
| Euro OTC                   | Neomycin sulfate | 130033-03        | 1       |
| Fagron                     | Neomycin sulfate | 12H23-N04        | 5       |
| Euro OTC                   | Neomycin sulfate | 1303033-01       | 12      |
| Euro OTC                   | Neomycin sulfate | 1303001-03       | 1       |
| Euro OTC                   | Neomycin sulfate | 1303033-02       | 12      |
| Phönix                     | Neomycin sulfate | 1303033-02       | 1       |
| Pfizer USA / Phönix        | Neomycin sulfate | 1303033-02       | 1       |
| Euro OTC                   | Neomycin sulfate | 1303033-03       | 15      |
| phoenix 13.11.14           | Neomycin sulfate | 1303033-03       | 1       |
| Caelo                      | Neomycin sulfate | 1303033-03       | 1       |
| Gehe                       | Neomycin sulfate | 1303033-03       | 1       |
| Land/Phönix                | Neomycin sulfate | 13062905         | 2       |
| Caelo                      | Neomycin sulfate | 13062905         | 2       |
| Caelo                      | Neomycin sulfate | 13062915         | 1       |
| Caelo                      | Neomycin sulfate | 13062922         | 1       |
| Caelo                      | Neomycin sulfate | 13062908         | 1       |
| caesar&loretz,AHC,7.3.16   | Neomycin sulfate | 13062923         | 1       |
| Fagron                     | Neomycin sulfate | 13D10-N05        | 9       |
| Caelo                      | Neomycin sulfate | 13D10N05         | 1       |
| Fagron                     | Neomycin sulfate | 13G09N07         | 2       |
| Fagron                     | Neomycin sulfate | 13G09-N07        | 14      |
|                            | Neomycin sulfate | 13G09-N07        | 1       |
| Fagron                     | Neomycin sulfate | 13K15-B33-288069 | 3       |
| Fagron                     | Neomycin sulfate | 13K15-B33-288073 | 3       |
| Fagron                     | Neomycin sulfate | 14A31B02         | 2       |
| Fagron                     | Neomycin sulfate | 13K15-b33-288069 | 1       |
| Fagron                     | Neomycin sulfate | 14A31-B02        | 2       |
| Fagron                     | Neomycin sulfate | 14A31-B02-294696 | 3       |
| Fagron                     | Neomycin sulfate | 14A31B02294696   | 1       |
| Caelo                      | Neomycin sulfate | 14A31-B02-294696 | 1       |
| Fagron                     | Neomycin sulfate | 14A31-B02-294697 | 1       |
| AHD                        | Neomycin sulfate | 14A31-B02-294698 | 2       |
| fargron                    | Neomycin sulfate | 14A31-B02-294698 | 1       |
| Fagron                     | Neomycin sulfate | 14A31-B02-294698 | 1       |
| Fagron                     | Neomycin sulfate | 14A31-B02-296724 | 1       |
| Fagron                     | Neomycin sulfate | 14C27-B05        | 1       |
| Fagron                     | Neomycin sulfate | 14A31-B02-302519 | 1       |
| Fagron                     | Neomycin sulfate | 14C27-B05-302517 | 1       |
| Taoasis/Phoenix            | Neomycin sulfate | 1502004-01       | 1       |
| HenryLamotte               | Neomycin sulfate | 1502004-01       | 3       |
| Euro/Phönix                | Neomycin sulfate | 1502004-01       | 1       |

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| Supplier                   | Substance        | Batch            | Spectra |
|----------------------------|------------------|------------------|---------|
| Caelo                      | Neomycin sulfate | 1502004-01       | 1       |
| Fagron                     | Neomycin sulfate | 1502004-01       | 1       |
| Euro OTC                   | Neomycin sulfate | 1502004-03       | 4       |
| Jenne                      | Neomycin sulfate | 15237602         | 1       |
| Caesar&Loretz,AHC,05.09... | Neomycin sulfate | 15237602         | 1       |
| Caelo                      | Neomycin sulfate | 15237602         | 1       |
| Caelo                      | Neomycin sulfate | 15298902         | 1       |
| Noweda                     | Neomycin sulfate | 15298902         | 1       |
| Caesar&Loretz/Noweda       | Neomycin sulfate | 15298904         | 1       |
| Fagron                     | Neomycin sulfate | 15J09-B04        | 1       |
| Fragon/Phoenix             | Neomycin sulfate | 15J09-B04322943  | 1       |
| Fagron                     | Neomycin sulfate | 15J09-B04-314015 | 2       |
| Fagron                     | Neomycin sulfate | 15J09-B04-314017 | 3       |
| Fagron                     | Neomycin sulfate | 15J09-B04314015  | 1       |
| Cealo/AHD                  | Neomycin sulfate | 15J09-B04-314017 | 1       |
| Euro OTC                   | Neomycin sulfate | 1601046-01       | 7       |
| Fagron                     | Neomycin sulfate | 15J27-B07        | 1       |
| Euro OTC                   | Neomycin sulfate | 160104601        | 1       |
| Caelo                      | Neomycin sulfate | 16122601         | 1       |
| Caelo                      | Neomycin sulfate | 16122612         | 2       |
| Caesar&Loretz GmbH,18.0... | Neomycin sulfate | 16122612         | 1       |
| Euro OTC                   | Neomycin sulfate | 16019046-01      | 1       |
| Fagron                     | Neomycin sulfate | 16A20-B10        | 1       |
| Caelo                      | Neomycin sulfate | 16122618         | 1       |
| Fagron                     | Neomycin sulfate | 16A20-B10-327433 | 1       |
| Fagron                     | Neomycin sulfate | 17B14-B08        | 1       |
| siehe WE-Prüfprotokoll     | Neomycin sulfate | 19/12            | 1       |
| Fagron                     | Neomycin sulfate | 16B10B50328165   | 1       |
| Gehe                       | Neomycin sulfate | 194A-01926       | 1       |
| Fagron                     | Neomycin sulfate | 4312I-01926      | 1       |
| Caelo                      | Neomycin sulfate | 5/AKD36          | 1       |
| Fagron                     | Neomycin sulfate | F08469           | 1       |
| Fagron                     | Neomycin sulfate | F08469           | 1       |
| Euro OTC                   | Neomycin sulfate | G73890           | 1       |
| Euro OTC                   | Neomycin sulfate | L34419           | 1       |
| Caelo                      | Neomycin sulfate | 563313062905     | 1       |
| Fagron                     | Neomycin sulfate | M71862           | 1       |
| Caelo                      | Neomycin sulfate | 9105316          | 1       |
| Fagron                     | Neomycin sulfate | 10121-N01        | 1       |
| Fagron                     | Neomycin sulfate | 11/19-N14        | 5       |
| Caesar & Loretz GmbH, 4... | Neomycin sulfate | 11/19-N14        | 1       |
| AHD                        | Neomycin sulfate | 11/19-N14        | 1       |
| Euro OTC                   | Neomycin sulfate | 1102043          | 2       |
| Euro OTC                   | Neomycin sulfate | 1102043-01       | 2       |
| Caelo                      | Neomycin sulfate | 1102043-02       | 1       |
| Gehe                       | Neomycin sulfate | 1102043-02       | 1       |
| aurica/phoenix             | Neomycin sulfate | 1102043-02       | 1       |
| EuRho                      | Neomycin sulfate | 1102043-02       | 1       |
| Alliance Healthcare        | Neomycin sulfate | 1102043-03       | 1       |
| Euro OTC                   | Neomycin sulfate | 1102043-03       | 4       |
| Anzag 13.06.2013           | Neomycin sulfate | 1102043-03       | 1       |
| Caelo                      | Neomycin sulfate | 1102043-03       | 2       |
| Fagron                     | Neomycin sulfate | 11C21-N10        | 1       |
| Caelo                      | Neomycin sulfate | 11C21-N10        | 1       |
| EuRho/Sanacorp             | Neomycin sulfate | 1102043-03       | 1       |
| Caelo                      | Neomycin sulfate | 12175401         | 6       |
| Caelo                      | Neomycin sulfate | 12276405         | 3       |
| Phönix Gotha               | Neomycin sulfate | 12C13-N04        | 1       |
| Caesar&Loretz,Phoenix      | Neomycin sulfate | 12C13-N04        | 1       |
| Fagron                     | Neomycin sulfate | 12C13-N04        | 4       |

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| Supplier                  | Substance        | Batch             | Spectra |
|---------------------------|------------------|-------------------|---------|
| Anzag                     | Neomycin sulfate | 12H20-N04         | 1       |
| Caelo                     | Neomycin sulfate | 12H23-N04         | 1       |
| Fagron                    | Neomycin sulfate | 12G09-N07         | 1       |
| Fagron                    | Neomycin sulfate | 12I19-N14         | 1       |
| Alliance Health 13.01.204 | Neomycin sulfate | 1303033-01        | 2       |
| phnoix                    | Neomycin sulfate | 130303301         | 1       |
| Ashland/Sanacorp          | Neomycin sulfate | 1303033-02        | 1       |
| Caelo                     | Neomycin sulfate | 1303033-02        | 1       |
|                           | Neomycin sulfate | 1303033-03        | 1       |
| Phönix                    | Neomycin sulfate | 13D10-N05         | 1       |
| Fagron                    | Neomycin sulfate | 13D10-N05         | 1       |
| Fagron                    | Neomycin sulfate | 13G09-N06         | 1       |
| Caelo                     | Neomycin sulfate | 13G09-N07         | 1       |
| Fagron                    | Neomycin sulfate | 13G09-N070129/340 | 1       |
| Gehe                      | Neomycin sulfate | 183360-0009       | 1       |
| Caelo                     | Neomycin sulfate | 24111203          | 1       |
| Caelo                     | Neomycin sulfate | 5/AKD35           | 1       |
| VDL;24.6.14; 3,55EUR      | Neomycin sulfate | 1303033-02        | 2       |
| Caelo                     | Neomycin sulfate | 12276415          | 1       |

- 69 357 spectra from 414 *Apo-Ident* customers from a total of 23 718 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Neomycin sulfate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Neomycin sulfate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 220           | 0              | 71 166        |
| <b>Type B</b> | 0              | 332           | 63             | 146 334       |
| <b>Type C</b> | 0              | 260           | 16             | 69 357        |

The substance/substance group *Neomycin sulfate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.2727 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 84.0506 % (> 83.2911 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 94.2029 % (> 93.1159 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to

exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21771     | 21771               | 0.00                         | 23.46                           |
| 21814     | 21814               | 0.00                         | 22.14                           |
| 21894     | 21894               | 0.00                         | 37.22                           |
| 21961     | 21771               | 6.14                         | 26.71                           |
| 22276     | 21814               | 4.01                         | 19.91                           |
| 22381     | 22381               | 0.00                         | 33.81                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Neostigmine bromide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20717-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Neostigmine bromide; Neostigmini bromidum

### Special notes

When selecting the *Neostigmine bromide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Neostigmine bromide*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate        |
|----------|---------------------|----------|-----------|---------|--------------------|
| Caelo    | Neostigmine brom... | 10144105 | 20717     | 40      | 20100616           |
| Caelo    | Neostigmine brom... | 12172304 | 20990     | 40      | 1403163            |
| Caelo    | Neostigmine brom... | 14256802 | 21816     | 40      | AR-15-FG-014460-01 |
| Caelo    | Neostigmine brom... | 15228101 | 21919     | 40      | 20151002           |
| Caelo    | Neostigmine brom... | 14256802 | 21816SI   | 40      | AR-15-FG-014460-01 |
| Caelo    | Neostigmine brom... | 15228101 | 21919SI   | 40      | 20151002           |



## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Neostigmine bromide*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 8 reference samples from the substance/substance group *Neostigmine bromide*.

| Supplier | Substance           | Batch    | Sample ID            | Spectra |
|----------|---------------------|----------|----------------------|---------|
| Caelo    | Neostigmine bromide | 14256802 | 21816 <sup>†</sup>   | 20      |
| Caelo    | Neostigmine bromide | 15228101 | 21919 <sup>†</sup>   | 20      |
| Caelo    | Neostigmine bromide | 171319   | 23369                | 40      |
| Caelo    | Neostigmine bromide | 17131901 | 23373                | 40      |
| Caelo    | Neostigmine bromide | 14256802 | 21816SI <sup>†</sup> | 20      |
| Caelo    | Neostigmine bromide | 15228101 | 21919SI <sup>†</sup> | 20      |
| Caelo    | Neostigmine bromide | 171319   | 23369SI              | 40      |
| Caelo    | Neostigmine bromide | 17131901 | 23373SI              | 40      |

- 146 489 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 14 spectra from 5 *Apo-Ident* customers from 9 batches from the substance/substance group *Neostigmine bromide*.

| Supplier | Substance           | Batch      | Spectra |
|----------|---------------------|------------|---------|
| Caelo    | Neostigmine bromide | 13177203   | 2       |
| Caelo    | Neostigmine bromide | 13177206   | 4       |
| Gehe     | Neostigmine bromide | 12172301   | 1       |
| Caelo    | Neostigmine bromide | 14256802   | 1       |
| Caelo    | Neostigmine bromide | 12172301   | 1       |
| Caelo    | Neostigmine bromide | 12172304   | 1       |
| Gehe     | Neostigmine bromide | 12172307   | 1       |
| Caelo    | Neostigmine bromide | 131772303B | 1       |
| Caelo    | Neostigmine bromide | 131772303A | 1       |
| Gehe     | Neostigmine bromide | 13177201   | 1       |

- 69 619 spectra from 414 *Apo-Ident* customers from a total of 23 792 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Neostigmine bromide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Neostigmine bromide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 240           | 0              | 146 489       |
| <b>Type C</b> | 0              | 14            | 0              | 69 619        |

The substance/substance group *Neostigmine bromide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20717     | 20990               | 4.48                         | 78.80                           |
| 20990     | 20990               | 0.00                         | 78.08                           |
| 21816     | 21816               | 0.00                         | 76.75                           |
| 21919     | 21816               | 5.17                         | 81.04                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Nicotinamide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20335-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Nicotinamide; Nicotinamidum; Nicotinoylamidum

### Special notes

When selecting the *Nicotinamide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Nicotinamide*:

| Supplier | Substance    | Batch      | Sample ID | Spectra | Certificate |
|----------|--------------|------------|-----------|---------|-------------|
| Caelo    | Nicotinamide | 13097506   | 21364     | 40      | 20130416    |
| Euro OTC | Nicotinamide | 1310025-01 | 21643     | 40      | 20131121    |
| Euro OTC | Nicotinamide | 1511010    | 22251     | 40      | 20151203*   |
| Euro OTC | Nicotinamide | 1601045    | 22374     | 40      | 20160210*   |
| Euro OTC | Nicotinamide | 1610019    | 22874     | 40      | 20161202*   |
| Caelo    | Nicotinamide | 163048     | 23050     | 40      | 20161123*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Nicotinamide*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 480 spectra of 13 reference samples from the substance/substance group *Nicotinamide*.

| Supplier | Substance    | Batch      | Sample ID          | Spectra |
|----------|--------------|------------|--------------------|---------|
| Fagron   | Nicotinamide | 10L21-N09  | 20335              | 40      |
| Fagron   | Nicotinamide | L11060228  | 20388              | 40      |
| Caelo    | Nicotinamide | 11001803   | 20399              | 40      |
| Euro OTC | Nicotinamide | 1003025-03 | 20407              | 40      |
| Euro OTC | Nicotinamide | 1108021-01 | 20577              | 40      |
| Caelo    | Nicotinamide | 11001809   | 20647              | 40      |
| Euro OTC | Nicotinamide | 1310025-01 | 21643 <sup>†</sup> | 20      |
| Euro OTC | Nicotinamide | 1511010    | 22251 <sup>†</sup> | 20      |
| Euro OTC | Nicotinamide | 1601045    | 22374 <sup>†</sup> | 20      |
| Caelo    | Nicotinamide | 161136     | 22434              | 60      |
| Caelo    | Nicotinamide | 161136     | 22625              | 40      |
| Caelo    | Nicotinamide | 163048     | 23038              | 40      |
| Euro OTC | Nicotinamide | 1707001    | 23555              | 40      |

- 146 249 spectra from a total of 3182 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B*

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 44 spectra from 24 *Apo-Ident* customers from 26 batches from the substance/substance group *Nicotinamide*.

| Supplier                   | Substance    | Batch         | Spectra |
|----------------------------|--------------|---------------|---------|
| Euro OTC                   | Nicotinamide | 11401052      | 1       |
| Caelo                      | Nicotinamide | 13097504      | 1       |
| Caelo                      | Nicotinamide | 13097506      | 1       |
| Phoenix                    | Nicotinamide | 1211031-02    | 1       |
| Fagron                     | Nicotinamide | 12J02-B03     | 1       |
| Euro OTC                   | Nicotinamide | 1310025-01    | 4       |
| Euro OTC                   | Nicotinamide | 131002501     | 1       |
| Caelo                      | Nicotinamide | 13352002      | 1       |
| Euro OTC                   | Nicotinamide | 1408019-01    | 4       |
| Caelo                      | Nicotinamide | 14246806      | 1       |
| Euro OTC                   | Nicotinamide | 1511010-01    | 1       |
| Euro OTC                   | Nicotinamide | 1503024-01    | 2       |
| Caelo                      | Nicotinamide | 1511010-01    | 1       |
| Euro OTC                   | Nicotinamide | 1601045-01    | 2       |
| Euro OTC                   | Nicotinamide | 1610019-01    | 3       |
| Caelo                      | Nicotinamide | 16304803      | 1       |
| Fagron                     | Nicotinamide | L14020084     | 1       |
| Fagron                     | Nicotinamide | 10L21-N09     | 1       |
| DSM Nutritional Prod./ ... | Nicotinamide | 1106044-01    | 1       |
| Euro OTC                   | Nicotinamide | 11208021      | 1       |
| Euro OTC                   | Nicotinamide | 1108021-01    | 1       |
| Euro OTC                   | Nicotinamide | 1108021-02    | 1       |
| Euro OTC                   | Nicotinamide | 1211031-01    | 2       |
| Noweda                     | Nicotinamide | 12133403      | 2       |
| Euro OTC                   | Nicotinamide | 1211031-02    | 1       |
| Caelo                      | Nicotinamide | 12133403      | 1       |
| Caelo                      | Nicotinamide | 12268302      | 1       |
| Gatt-Koller                | Nicotinamide | 221406112411  | 1       |
| Euro OTC                   | Nicotinamide | 1106044-01    | 2       |
| Gatt-Koller                | Nicotinamide | 4456/10104110 | 1       |
| VDL;16.04.15;5,60EUR       | Nicotinamide | 1408019-01    | 1       |

- 69 589 spectra from 414 *Apo-Ident* customers from a total of 23 775 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Nicotinamide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Nicotinamide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following

table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 240           | 0              | 71 146        |
| Type B | 0              | 480           | 0              | 146 249       |
| Type C | 0              | 44            | 0              | 69 589        |

The substance/substance group *Nicotinamide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.7500 %) |
| Type C | 100.0000 % (> 99.8813 %) | 100.0000 % (> 86.3636 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21364     | 22251               | 5.66                         | 69.53                           |
| 21643     | 22374               | 2.15                         | 68.78                           |
| 22251     | 22251               | 0.00                         | 69.56                           |
| 22374     | 22374               | 0.00                         | 68.26                           |
| 22874     | 22874               | 0.00                         | 69.51                           |
| 23050     | 23050               | 0.00                         | 69.71                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Nicotinic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20383-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Nicotinic acid; Acidum nicotinicum

### Special notes

When selecting the *Nicotinic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Nicotinic acid*:

| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate        |
|----------|----------------|------------------|-----------|---------|--------------------|
| Fagron   | Nicotinic acid | 14E01-B09-293947 | 21692     | 40      | AR-15-FG-008938-01 |
| Fagron   | Nicotinic acid | 16H19-B02-330121 | 23225     | 40      | AR-17-FG-016013-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Nicotinic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *Nicotinic acid*.

| Supplier | Substance      | Batch            | Sample ID          | Spectra |
|----------|----------------|------------------|--------------------|---------|
| Fagron   | Nicotinic acid | L10070324        | 20383              | 40      |
| Fagron   | Nicotinic acid | 14E01-B09-293947 | 21692 <sup>†</sup> | 20      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 2 spectra from 1 *Apo-Ident* customers from 2 batches from the substance/substance group *Nicotinic acid*.

| Supplier  | Substance      | Batch     | Spectra |
|-----------|----------------|-----------|---------|
| AppliChem | Nicotinic acid | 2Q006387  | 1       |
| Fagron    | Nicotinic acid | 14E01-B09 | 1       |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Nicotinic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Nicotinic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 2             | 0              | 69 631        |

The substance/substance group *Nicotinic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21692     | 21692               | 0.00                         | 90.00                           |
| 23225     | 23225               | 0.00                         | 85.15                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das

alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Nitrofurantoin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20698-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Nitrofurantoin; Nitrofurantoinum

### Special notes

When selecting the *Nitrofurantoin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Nitrofurantoin*:

| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate        |
|----------|----------------|------------------|-----------|---------|--------------------|
| Fagron   | Nitrofurantoin | 12C30-N03        | 20698     | 40      | 1401461            |
| Fagron   | Nitrofurantoin | 11K-21-N23       | 20836     | 40      | 20111128           |
| Fagron   | Nitrofurantoin | 12C30-N03        | 20837     | 40      | 20120417           |
| Fagron   | Nitrofurantoin | 13B28-N07        | 21091     | 40      | 20130304           |
| Fagron   | Nitrofurantoin | 11I07-N11        | 21273     | 40      | 20110829           |
| Fagron   | Nitrofurantoin | 15J15-B06-315225 | 22257     | 40      | AR-16-FG-003763-01 |
| Fagron   | Nitrofurantoin | 15J15-B06-315225 | 22322     | 40      | 20151028           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 280 spectra of 7 reference samples from the substance/substance group *Nitrofurantoin*. These samples are listed above in the [calibration samples](#) section.
- 71 106 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 40 spectra of 2 reference samples from the substance/substance group *Nitrofurantoin*.

| Supplier | Substance      | Batch            | Sample ID          | Spectra |
|----------|----------------|------------------|--------------------|---------|
| Fagron   | Nitrofurantoin | 15J15-B06-315225 | 22257 <sup>†</sup> | 20      |
| Fagron   | Nitrofurantoin | 15J15-B06-315225 | 22322 <sup>†</sup> | 20      |

- 146 689 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 17 spectra from 11 *Apo-Ident* customers from 13 batches from the substance/substance group *Nitrofurantoin*.

| Supplier | Substance      | Batch   | Spectra |
|----------|----------------|---------|---------|
| Fagron   | Nitrofurantoin | 3071403 | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier              | Substance      | Batch            | Spectra |
|-----------------------|----------------|------------------|---------|
| Fagron                | Nitrofurantoin | 11F07-N06        | 3       |
| Fagron                | Nitrofurantoin | 71/14            | 1       |
| Fagron                | Nitrofurantoin | 13A08-N01        | 1       |
| Fagron                | Nitrofurantoin | 13D10-N03        | 1       |
| Fagron                | Nitrofurantoin | 13B28-N07        | 1       |
| Apotheke am Lindenhof | Nitrofurantoin | 15J15-B06        | 1       |
| Fagron                | Nitrofurantoin | 15J15-B06        | 1       |
| Fagron                | Nitrofurantoin | 15J15-B06-313939 | 1       |
| Fagron                | Nitrofurantoin | 15J15-B06-315225 | 1       |
| Fagron                | Nitrofurantoin | 15J15-B06-317250 | 2       |
| Fagron                | Nitrofurantoin | 201203080296     | 1       |
| Fagron                | Nitrofurantoin | 12C30-N03        | 1       |
| Fagron                | Nitrofurantoin | 2714I-03527      | 1       |

- 69 616 spectra from 414 *Apo-Ident* customers from a total of 23 788 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Nitrofurantoin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Nitrofurantoin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 280           | 0              | 71 106        |
| <b>Type B</b> | 0              | 40            | 0              | 146 689       |
| <b>Type C</b> | 0              | 15            | 2              | 69 616        |

The substance/substance group *Nitrofurantoin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.8571 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 85.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20698     | 20698               | 0.00                         | 69.18                           |
| 20836     | 20698               | 8.03                         | 68.05                           |
| 20837     | 20698               | 6.67                         | 67.79                           |
| 21091     | 22257               | 11.65                        | 85.99                           |
| 21273     | 20698               | 11.80                        | 68.92                           |
| 22257     | 22257               | 0.00                         | 80.41                           |
| 22322     | 22257               | 3.24                         | 79.64                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Non-ionic emulsifying alcohol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20467-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Non-ionic emulsifying alcohol; Alkoholes emulsificantes nonionici

### Special notes

When selecting the *Non-ionic emulsifying alcohol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Non-ionic emulsifying alcohol*:

| Supplier | Substance           | Batch         | Sample ID | Spectra | Certificate |
|----------|---------------------|---------------|-----------|---------|-------------|
| Caelo    | Non-ionic emulsi... | 13413001      | 21069     | 40      | 1405257     |
| apomix   | Non-ionic emulsi... | NS-8350010216 | 23274     | 40      | 20160718    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Non-ionic emulsifying alcohol*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 210 spectra of 5 reference samples from the substance/substance group *Non-ionic emulsifying alcohol*.

| Supplier  | Substance                     | Batch    | Sample ID | Spectra |
|-----------|-------------------------------|----------|-----------|---------|
| Bombastus | Non-ionic emulsifying alcohol | 238393   | 20183     | 50      |
| Bombastus | Non-ionic emulsifying alcohol | 267575   | 20467     | 40      |
| Caelo     | Non-ionic emulsifying alcohol | 13413001 | 21524     | 40      |
| Caelo     | Non-ionic emulsifying alcohol | 162231   | 22745     | 40      |
| Caelo     | Non-ionic emulsifying alcohol | 171836   | 23576     | 40      |

- 146 519 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 12 spectra from 9 *Apo-Ident* customers from 7 batches from the substance/substance group *Non-ionic emulsifying alcohol*.

| Supplier  | Substance                     | Batch  | Spectra |
|-----------|-------------------------------|--------|---------|
| Euro OTC  | Non-ionic emulsifying alcohol | 278281 | 2       |
| Bombastus | Non-ionic emulsifying alcohol | 284009 | 2       |

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| Supplier  | Substance                     | Batch    | Spectra |
|-----------|-------------------------------|----------|---------|
| Bombastus | Non-ionic emulsifying alcohol | 292319   | 2       |
| Caelo     | Non-ionic emulsifying alcohol | 12254402 | 1       |
| Bombastus | Non-ionic emulsifying alcohol | 267575   | 3       |
| Caelo     | Non-ionic emulsifying alcohol | 21091302 | 1       |
| Bombastus | Non-ionic emulsifying alcohol | 274059   | 1       |

- 69 621 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Non-ionic emulsifying alcohol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Non-ionic emulsifying alcohol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 210           | 0              | 146 519       |
| <b>Type C</b> | 0              | 11            | 1              | 69 621        |

The substance/substance group *Non-ionic emulsifying alcohol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.1429 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21069     | 21069               | 0.00                         | 28.19                           |
| 23274     | 21069               | 11.18                        | 32.14                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Norethisterone acetate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20797-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Norethisterone acetate; Norethisteroni acetas; Norethisteronum aceticum

### Special notes

When selecting the *Norethisterone acetate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Norethisterone acetate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Fagron   | Norethisterone a... | 12L14-N03  | 20797     | 40      | 1401558     |
| Euro OTC | Norethisterone a... | 1306033-01 | 21627     | 20      | 1511684     |
| Caelo    | Norethisterone a... | 15417004   | 23122     | 40      | 1711489     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 100 spectra of 3 reference samples from the substance/substance group *Norethisterone acetate*. These samples are listed above in the [calibration samples](#) section.
- 71 286 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 3 reference samples from the substance/substance group *Norethisterone acetate*.

| Supplier | Substance              | Batch            | Sample ID          | Spectra |
|----------|------------------------|------------------|--------------------|---------|
| Fagron   | Norethisterone acetate | 11C10-N03        | 20230              | 40      |
| Euro OTC | Norethisterone acetate | 1306033-01       | 21627 <sup>†</sup> | 40      |
| Fagron   | Norethisterone acetate | 14H29-B03-325225 | 23171              | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 15 spectra from 10 *Apo-Ident* customers from 11 batches from the substance/substance group *Norethisterone acetate*.

| Supplier  | Substance              | Batch     | Spectra |
|-----------|------------------------|-----------|---------|
| Bombastus | Norethisterone acetate | 13J08-N04 | 1       |
| Fagron    | Norethisterone acetate | 13J08-N04 | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier | Substance              | Batch            | Spectra |
|----------|------------------------|------------------|---------|
| Caelo    | Norethisterone acetate | 13J08-N04        | 1       |
| Fagron   | Norethisterone acetate | 13D19-N06        | 1       |
| Fagron   | Norethisterone acetate | 14d08-b01-292736 | 1       |
| Fagron   | Norethisterone acetate | 14D08-B01-292738 | 1       |
| Fagron   | Norethisterone acetate | 14h29-b03-310697 | 1       |
| Fagron   | Norethisterone acetate | 11H22-N03        | 2       |
| Fagron   | Norethisterone acetate | 23071509         | 1       |
| Fagron   | Norethisterone acetate | 10L22-N01        | 1       |
| Fagron   | Norethisterone acetate | 22061206         | 1       |
| Fagron   | Norethisterone acetate | 12C06-N10        | 2       |
| Fagron   | Norethisterone acetate | 13D19-No6        | 1       |

- 69 618 spectra from 414 *Apo-Ident* customers from a total of 23 790 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Norethisterone acetate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Norethisterone acetate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 100           | 0              | 71 286        |
| <b>Type B</b> | 0              | 116           | 4              | 146 609       |
| <b>Type C</b> | 0              | 15            | 0              | 69 618        |

The substance/substance group *Norethisterone acetate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 96.6667 % (> 94.1667 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested

reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20797     | 20797               | 0.00                         | 15.28                           |
| 21627     | 21627               | 0.00                         | 12.69                           |
| 23122     | 23122               | 0.00                         | 9.32                            |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Octenidine dihydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20759-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Octenidine dihydrochloride; Octenidini dihydrochloridum

### Special notes

When selecting the *Octenidine dihydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Octenidine dihydrochloride*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Octenidine dihyd... | 12115202 | 20759     | 40      | 20120511    |
| Caelo    | Octenidine dihyd... | 13071407 | 20988     | 40      | 1407345     |
| Caelo    | Octenidine dihyd... | 13166806 | 21331     | 40      | 20130718    |
| Caelo    | Octenidine dihyd... | 15275502 | 21888     | 40      | 20150910    |
| Caelo    | Octenidine dihyd... | 15356601 | 21947     | 40      | 1604116     |
| Caelo    | Octenidine dihyd... | 163355   | 23309     | 40      | 20170403*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Octenidine dihydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 340 spectra of 8 reference samples from the substance/substance group *Octenidine dihydrochloride*.

| Supplier | Substance                  | Batch    | Sample ID          | Spectra |
|----------|----------------------------|----------|--------------------|---------|
| Caelo    | Octenidine dihydrochloride | 15275502 | 21888 <sup>†</sup> | 20      |
| Caelo    | Octenidine dihydrochloride | 15356601 | 21947 <sup>†</sup> | 20      |
| Caelo    | Octenidine dihydrochloride | 160330   | 22485              | 60      |
| Caelo    | Octenidine dihydrochloride | 170423   | 23307              | 40      |
| Caelo    | Octenidine dihydrochloride | 15275502 | 21888SI            | 60      |
| Caelo    | Octenidine dihydrochloride | 15356601 | 21947SI            | 60      |
| Caelo    | Octenidine dihydrochloride | 170423   | 23307SI            | 40      |
| Caelo    | Octenidine dihydrochloride | 163355   | 23309SI            | 40      |

- 146 389 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 76 spectra from 47 *Apo-Ident* customers from 36 batches from the substance/substance group *Octenidine dihydrochloride*.

| Supplier                   | Substance                  | Batch       | Spectra |
|----------------------------|----------------------------|-------------|---------|
| Caelo                      | Octenidine dihydrochloride | 13166801    | 1       |
| Caelo                      | Octenidine dihydrochloride | 13166808    | 2       |
| Löwen City-Apotheke Bar... | Octenidine dihydrochloride | 2042015     | 1       |
| Caelo                      | Octenidine dihydrochloride | 816M-03732  | 1       |
| Caelo                      | Octenidine dihydrochloride | 13166810    | 1       |
| Apomix/Noweda              | Octenidine dihydrochloride | 13166813    | 1       |
| Caelo                      | Octenidine dihydrochloride | 15006202    | 4       |
| Caelo                      | Octenidine dihydrochloride | 15006207    | 3       |
| Caelo/Sanacorp             | Octenidine dihydrochloride | 15006207    | 1       |
| Caelo                      | Octenidine dihydrochloride | 15006203    | 1       |
| Caesar & Loretz GmbH       | Octenidine dihydrochloride | 15006210    | 1       |
| Caelo                      | Octenidine dihydrochloride | 15275502    | 3       |
| Caelo                      | Octenidine dihydrochloride | 15275503    | 2       |
| Caelo                      | Octenidine dihydrochloride | 1515E-03732 | 1       |
| Caelo                      | Octenidine dihydrochloride | 15275504    | 1       |
| Caelo                      | Octenidine dihydrochloride | 15356601    | 3       |
| Caelo                      | Octenidine dihydrochloride | 15356603    | 1       |
| Caelo                      | Octenidine dihydrochloride | 15356703    | 7       |
| Caelo                      | Octenidine dihydrochloride | 16032803    | 4       |
| Caelo                      | Octenidine dihydrochloride | 16032901    | 1       |
| Caelo                      | Octenidine dihydrochloride | 16032902    | 3       |
| Caelo                      | Octenidine dihydrochloride | 16032903    | 1       |
| Caelo                      | Octenidine dihydrochloride | 16032909    | 4       |
| Caelo                      | Octenidine dihydrochloride | 16033001    | 2       |
| Caelo                      | Octenidine dihydrochloride | 16032910    | 3       |
| Caelo                      | Octenidine dihydrochloride | 16277802    | 4       |
| Celo                       | Octenidine dihydrochloride | 16277802    | 1       |
| Caelo                      | Octenidine dihydrochloride | 16033002    | 1       |
| Caelo                      | Octenidine dihydrochloride | 16302910    | 1       |
| Caelo                      | Octenidine dihydrochloride | 16325304    | 3       |
| Caelo                      | Octenidine dihydrochloride | 16325408    | 2       |
| Caesar&Loretz GmbH, 14...  | Octenidine dihydrochloride | 17042302    | 1       |
| Caelo                      | Octenidine dihydrochloride | 16325406    | 1       |
| Caelo                      | Octenidine dihydrochloride | 16325305    | 1       |
| Caelo                      | Octenidine dihydrochloride | 17042304    | 4       |
| Caelo                      | Octenidine dihydrochloride | 17042903    | 2       |
| Caelo                      | Octenidine dihydrochloride | 17042305    | 1       |
| Caelo                      | Octenidine dihydrochloride | 15356602    | 1       |

- 69 557 spectra from 414 *Apo-Ident* customers from a total of 23 766 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Octenidine dihydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Octenidine dihydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 340           | 0              | 146 389       |
| <b>Type C</b> | 0              | 76            | 0              | 69 557        |

The substance/substance group *Octenidine dihydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.2353 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 92.1053 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20759     | 23309               | 5.45                         | 28.86                           |
| 20988     | 20988               | 0.00                         | 28.60                           |
| 21331     | 21947               | 5.98                         | 31.38                           |
| 21888     | 21947               | 4.09                         | 44.79                           |
| 21947     | 21947               | 0.00                         | 38.38                           |
| 23309     | 23309               | 0.00                         | 27.40                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ofloxacin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21047-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ofloxacin; Ofloxacinum

### Special notes

When selecting the *Ofloxacin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ofloxacin*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Fagron   | Ofloxacin | 13A17-N01        | 21047     | 40      | 1403155     |
| Fagron   | Ofloxacin | 15H19-B01-312926 | 21918     | 40      | 20151006    |
| Fagron   | Ofloxacin | 15H19-B01-325226 | 23090     | 40      | 1707611     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Ofloxacin*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 270 spectra of 6 reference samples from the substance/substance group *Ofloxacin*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Fagron   | Ofloxacin | 13A17-N01        | 21052              | 40      |
| Fagron   | Ofloxacin | 13A17-N01        | 21811              | 60      |
| Fagron   | Ofloxacin | 15H19-B01-312926 | 21918 <sup>†</sup> | 20      |
| Fagron   | Ofloxacin | 13A17-N01        | 21811SI            | 60      |
| Fagron   | Ofloxacin | 15H19-B01-312926 | 21918SI            | 60      |
| Fagron   | Ofloxacin | 15H19-B01-325226 | 23090SI            | 30      |

- 146 459 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 3 spectra from 2 *Apo-Ident* customers from 3 batches from the substance/substance group *Ofloxacin*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance | Batch            | Spectra |
|----------|-----------|------------------|---------|
| Fagron   | Ofloxacin | 13A17-N01        | 1       |
| Caelo    | Ofloxacin | 15H19-B01        | 1       |
| Fagron   | Ofloxacin | 15H19-B01-314470 | 1       |

- 69 630 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ofloxacin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ofloxacin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 254           | 16             | 146 459       |
| <b>Type C</b> | 0              | 3             | 0              | 69 630        |

The substance/substance group *Ofloxacin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 94.0741 % (> 92.9630 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8817 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21047     | 21047               | 0.00                         | 21.60                           |
| 21918     | 23090               | 14.66                        | 31.59                           |
| 23090     | 23090               | 0.00                         | 19.84                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Omeprazole**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21098-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Omeprazole; Omeprazolum

### Special notes

When selecting the *Omeprazole* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Omeprazole*:

| Supplier  | Substance  | Batch            | Sample ID | Spectra | Certificate |
|-----------|------------|------------------|-----------|---------|-------------|
| Molekular | Omeprazole | 150908           | 21098     | 40      | 1405656     |
| Inresa    | Omeprazole | OPFP14017        | 21787     | 40      | 1507407     |
| Fagron    | Omeprazole | 15K12-B02-314608 | 22890     | 40      | 20151124    |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Omeprazole*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 260 spectra of 6 reference samples from the substance/substance group *Omeprazole*.

| Supplier | Substance  | Batch              | Sample ID          | Spectra |
|----------|------------|--------------------|--------------------|---------|
| Inresa   | Omeprazole | OPFP14017          | 21787 <sup>†</sup> | 20      |
| Inresa   | Omeprazole | OPFP14017          | 21796              | 60      |
| Inresa   | Omeprazole | OPFP14017          | 22284              | 60      |
| Fagron   | Omeprazole | 15K12-B02-314608   | 22740              | 40      |
| Fagron   | Omeprazole | 16I20-B03-328940   | 23272              | 40      |
| Inresa   | Omeprazole | OPFP14017/21072016 | 23273              | 40      |

- 146 469 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 6 spectra from 6 *Apo-Ident* customers from 4 batches from the substance/substance group *Omeprazole*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier | Substance  | Batch            | Spectra |
|----------|------------|------------------|---------|
| Fagron   | Omeprazole | 15B26-B40-305669 | 2       |
| Fagron   | Omeprazole | 15K12-B02        | 1       |
| Fagron   | Omeprazole | 15K12-B02-314608 | 2       |
| Fagron   | Omeprazole | OPFP16030        | 1       |

- 69 627 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

### Validation results

The validation runs checked whether the substance/substance group *Omeprazole* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Omeprazole* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 260           | 0              | 146 469       |
| <b>Type C</b> | 0              | 5             | 1              | 69 627        |

The substance/substance group *Omeprazole* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.6923 %) |
| <b>Type C</b> | 100.0000 % (> 99.8815 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21098     | 21098               | 0.00                         | 62.81                           |
| 21787     | 21787               | 0.00                         | 60.20                           |
| 22890     | 21787               | 4.78                         | 62.00                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ornithine aspartate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20842-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ornithine aspartate; Ornithini aspartas; Ornithinum asparticum

### Special notes

When selecting the *Ornithine aspartate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ornithine aspartate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Ornithine aspart... | L1304034-01      | 20842     | 40      | 1402571     |
| Fagron   | Ornithine aspart... | 14A20-B07-296093 | 21694     | 30      | 1506279     |
| Euro OTC | Ornithine aspart... | 1312030-01       | 21710     | 40      | 1506280     |
| Fagron   | Ornithine aspart... | 14I24-B04-307758 | 22600     | 40      | 20141110    |
| Euro OTC | Ornithine aspart... | 1611018          | 22924     | 40      | 20161213*   |
| Euro OTC | Ornithine aspart... | 1611018-01       | 23198     | 40      | 20161213    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 230 spectra of 6 reference samples from the substance/substance group *Ornithine aspartate*. These samples are listed above in the [calibration samples](#) section.
- 71 156 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 115 spectra of 4 reference samples from the substance/substance group *Ornithine aspartate*.

| Supplier | Substance           | Batch            | Sample ID          | Spectra |
|----------|---------------------|------------------|--------------------|---------|
| Euro OTC | Ornithine aspartate | L1107045-01      | 20439              | 40      |
| Fagron   | Ornithine aspartate | 14A20-B07-296093 | 21694 <sup>†</sup> | 15      |
| Euro OTC | Ornithine aspartate | 1312030-01       | 21710 <sup>†</sup> | 20      |
| Fagron   | Ornithine aspartate | 14I24-B04-307758 | 22599              | 40      |

- 146 614 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 4 spectra from 1 *Apo-Ident* customers from 3 batches from the substance/substance group *Ornithine aspartate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance           | Batch        | Spectra |
|----------|---------------------|--------------|---------|
| Euro OTC | Ornithine aspartate | 1501049-01   | 1       |
| Euro OTC | Ornithine aspartate | L1304034-01  | 2       |
| Euro OTC | Ornithine aspartate | L-1304034-01 | 1       |

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ornithine aspartate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ornithine aspartate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 230           | 0              | 71 156        |
| <b>Type B</b> | 0              | 75            | 40             | 146 614       |
| <b>Type C</b> | 0              | 1             | 3              | 69 629        |

The substance/substance group *Ornithine aspartate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.3913 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 65.2174 % (> 62.6087 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20842     | 20842               | 0.00                         | 66.25                           |
| 21694     | 21694               | 0.00                         | 54.38                           |

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| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21710            | 21710                      | 0.00                                | 43.56                                  |
| 22600            | 21710                      | 10.54                               | 44.70                                  |
| 22924            | 22924                      | 0.00                                | 48.19                                  |
| 23198            | 21694                      | 8.29                                | 55.99                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ornithine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20389-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ornithine hydrochloride; Ornithini hydrochloridum; Ornithinum hydrochloricum

### Special notes

When selecting the *Ornithine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ornithine hydrochloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Fagron   | Ornithine hydroc... | 13A03-N05  | 20967     | 40      | 1403094     |
| Euro OTC | Ornithine hydroc... | 1307028-01 | 21622     | 80      | 20130813    |
| Euro OTC | Ornithine hydroc... | 1605011    | 22573     | 40      | 20160601*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 3 reference samples from the substance/substance group *Ornithine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 5 reference samples from the substance/substance group *Ornithine hydrochloride*.

| Supplier | Substance               | Batch      | Sample ID          | Spectra |
|----------|-------------------------|------------|--------------------|---------|
| Fagron   | Ornithine hydrochloride | L11050156  | 20389              | 40      |
| Euro OTC | Ornithine hydrochloride | 1307028-01 | 21622 <sup>†</sup> | 40      |
| Euro OTC | Ornithine hydrochloride | 1612009    | 22923              | 40      |
| Euro OTC | Ornithine hydrochloride | 1612009-01 | 23009              | 40      |
| Euro OTC | Ornithine hydrochloride | 1704006    | 23159              | 40      |

- 146 529 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 8 spectra from 3 *Apo-Ident* customers from 8 batches from the substance/substance group *Ornithine hydrochloride*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier  | Substance               | Batch       | Spectra |
|-----------|-------------------------|-------------|---------|
| Fagron    | Ornithine hydrochloride | 13/23-No5   | 1       |
| unbekannt | Ornithine hydrochloride | 15000639    | 1       |
| Fagron    | Ornithine hydrochloride | 15A13-B03   | 1       |
| Fagron    | Ornithine hydrochloride | 13A03-N05   | 1       |
| Euro OTC  | Ornithine hydrochloride | 516Q-03475  | 1       |
| Euro OTC  | Ornithine hydrochloride | 315E-03475  | 1       |
| Euro OTC  | Ornithine hydrochloride | 4712A-03475 | 1       |
| Euro OTC  | Ornithine hydrochloride | 1014I-03475 | 1       |

- 69 625 spectra from 414 *Apo-Ident* customers from a total of 23 793 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

### Validation results

The validation runs checked whether the substance/substance group *Ornithine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ornithine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 200           | 0              | 146 529       |
| <b>Type C</b> | 0              | 8             | 0              | 69 625        |

The substance/substance group *Ornithine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20967     | 20967               | 0.00                         | 77.14                           |
| 21622     | 20967               | 2.83                         | 78.47                           |
| 22573     | 22573               | 0.00                         | 79.30                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Oxalic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20458-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Oxalic acid; Acidum oxalicum cryst.

### Special notes

When selecting the *Oxalic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Oxalic acid*:

| Supplier | Substance   | Batch    | Sample ID | Spectra | Certificate      |
|----------|-------------|----------|-----------|---------|------------------|
| Caelo    | Oxalic acid | 13353901 | 21042     | 40      | 20131029         |
| Caelo    | Oxalic acid | 12212410 | 21066     | 40      | 1403223          |
| Caelo    | Oxalic acid | 12147007 | 21068     | 40      | 1405523          |
| Caelo    | Oxalic acid | 13353918 | 21774     | 40      | 20131029         |
| Caelo    | Oxalic acid | 153999   | 22488     | 40      | nicht verfügbar* |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Oxalic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 320 spectra of 8 reference samples from the substance/substance group *Oxalic acid*.

| Supplier | Substance   | Batch    | Sample ID          | Spectra |
|----------|-------------|----------|--------------------|---------|
| Caelo    | Oxalic acid | 11372701 | 20458              | 40      |
| Caelo    | Oxalic acid | 11098216 | 20462              | 40      |
| Caelo    | Oxalic acid | 13353905 | 21453              | 60      |
| Caelo    | Oxalic acid | 13353918 | 21774 <sup>†</sup> | 20      |
| Caelo    | Oxalic acid | 160502   | 22487              | 60      |
| Caelo    | Oxalic acid | 153999   | 22488 <sup>†</sup> | 20      |
| Caelo    | Oxalic acid | 171140   | 23287              | 40      |
| Caelo    | Oxalic acid | 171140   | 23688              | 40      |

- 146 409 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 22 spectra from 18 *Apo-Ident* customers from 20 batches from the substance/substance group *Oxalic acid*.

| Supplier                   | Substance   | Batch       | Spectra |
|----------------------------|-------------|-------------|---------|
| Caelo                      | Oxalic acid | 914E-01039  | 1       |
| Noweda                     | Oxalic acid | 12212402    | 1       |
| Caelo                      | Oxalic acid | 10383104    | 1       |
| Caelo                      | Oxalic acid | 12212406    | 1       |
| Caelo                      | Oxalic acid | 12212407    | 1       |
| Caelo                      | Oxalic acid | 12212411    | 1       |
| Caelo                      | Oxalic acid | 13195408    | 1       |
| Caelo                      | Oxalic acid | 13353905    | 2       |
| Caelo                      | Oxalic acid | 13195414    | 1       |
| Caelo                      | Oxalic acid | 13353901    | 1       |
| Caelo                      | Oxalic acid | 13353907    | 2       |
| Caelo                      | Oxalic acid | 13353910    | 1       |
| Caelo                      | Oxalic acid | 13353915    | 1       |
| Caelo                      | Oxalic acid | 14334703    | 1       |
| Caesar&Loretz GmbH/ All... | Oxalic acid | 13353920    | 1       |
| Caelo                      | Oxalic acid | 12147010    | 1       |
| sanacorp                   | Oxalic acid | 11098213    | 1       |
| Caelo                      | Oxalic acid | 4812U-01039 | 1       |
| Nachprüfung                | Oxalic acid |             | 1       |
| Caelo                      | Oxalic acid | 13195413    | 1       |

- 69 611 spectra from 414 *Apo-Ident* customers from a total of 23 782 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Oxalic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Oxalic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 195           | 5              | 71 186        |
| <b>Type B</b> | 0              | 319           | 1              | 146 409       |
| <b>Type C</b> | 0              | 22            | 0              | 69 611        |

The substance/substance group *Oxalic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 97.5000 % (> 96.0000 %)  |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.6875 % (> 98.7500 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 72.7273 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21042     | 21066               | 4.33                         | 76.33                           |
| 21066     | 21066               | 0.00                         | 84.61                           |
| 21068     | 21068               | 0.00                         | 86.09                           |
| 21774     | 21066               | 3.02                         | 79.79                           |
| 22488     | 22488               | 0.00                         | 78.30                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Oxybuprocaine hydrochloride</b>                              |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20958-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Oxybuprocaine hydrochloride; Oxybuprocaini hydrochloridum; Oxybuprocainum hydrochloricum

### Special notes

When selecting the *Oxybuprocaine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Oxybuprocaine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Oxybuprocaine hy... | 13D16-N12        | 20958     | 40      | 1402060            |
| Fagron   | Oxybuprocaine hy... | 13J24-B07-295015 | 21799     | 40      | AR-15-FG-014812-02 |
| Fagron   | Oxybuprocaine hy... | 15A26-B07-306787 | 21922     | 40      | 20150203           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Oxybuprocaine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 5 reference samples from the substance/substance group *Oxybuprocaine hydrochloride*.

| Supplier    | Substance                   | Batch            | Sample ID          | Spectra |
|-------------|-----------------------------|------------------|--------------------|---------|
| zu erfassen | Oxybuprocaine hydrochloride | pending          | 20159              | 40      |
| Fagron      | Oxybuprocaine hydrochloride | 13J24-B07-295015 | 21799 <sup>†</sup> | 20      |
| Fagron      | Oxybuprocaine hydrochloride | 15A26-B07-306787 | 21922 <sup>†</sup> | 20      |
| Fagron      | Oxybuprocaine hydrochloride | 13J24-B07-295015 | 21799SI            | 60      |
| Fagron      | Oxybuprocaine hydrochloride | 15A26-B07-306787 | 21922SI            | 60      |

- 146 529 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 15 spectra from 8 *Apo-Ident* customers from 10 batches from the substance/substance group *Oxybuprocaine hydrochloride*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier | Substance                   | Batch            | Spectra |
|----------|-----------------------------|------------------|---------|
| Fagron   | Oxybuprocaine hydrochloride | 13C01-N01        | 4       |
| Fagron   | Oxybuprocaine hydrochloride | 13H13-N050001/18 | 1       |
| Fagron   | Oxybuprocaine hydrochloride | 13J24B07295015   | 1       |
| Caelo    | Oxybuprocaine hydrochloride | 14G21B02300384   | 1       |
| Fagron   | Oxybuprocaine hydrochloride | 15A26-B07        | 1       |
| Fagron   | Oxybuprocaine hydrochloride | 12L19N01         | 1       |
| Fagron   | Oxybuprocaine hydrochloride | 13h13-n05        | 2       |
| Klenk    | Oxybuprocaine hydrochloride | 3613M-07321      | 1       |
| Fagron   | Oxybuprocaine hydrochloride | 3613N-07321      | 1       |
| Fagron   | Oxybuprocaine hydrochloride | 4612M-03639      | 2       |

- 69 618 spectra from 414 *Apo-Ident* customers from a total of 23 791 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Oxybuprocaine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Oxybuprocaine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 162           | 38             | 146 529       |
| <b>Type C</b> | 0              | 13            | 2              | 69 618        |

The substance/substance group *Oxybuprocaine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 81.0000 % (> 79.5000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20958     | 20958               | 0.00                         | 40.17                           |
| 21799     | 21799               | 0.00                         | 41.23                           |
| 21922     | 20958               | 9.13                         | 38.57                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | Oxybutynin hydrochloride                                        |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20565-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Oxybutynin hydrochloride; Oxybutynini hydrochloridum; Oxybutyninum hydrochloricum

### Special notes

When selecting the *Oxybutynin hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Oxybutynin hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Oxybutynin hydro... | 13H26-B03-290572 | 21543     | 40      | AR-15-FG-002173-01 |
| Fagron   | Oxybutynin hydro... | 14A29-B09-293841 | 21704     | 30      | 20140227           |
| Fagron   | Oxybutynin hydro... | 14I16-B03-312059 | 22732     | 40      | 20141007           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 110 spectra of 3 reference samples from the substance/substance group *Oxybutynin hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 276 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 155 spectra of 4 reference samples from the substance/substance group *Oxybutynin hydrochloride*.

| Supplier | Substance                | Batch            | Sample ID          | Spectra |
|----------|--------------------------|------------------|--------------------|---------|
| Fagron   | Oxybutynin hydrochloride | 12D24-N07        | 20565              | 80      |
| Fagron   | Oxybutynin hydrochloride | 13H26-B03-290572 | 21543 <sup>†</sup> | 20      |
| Fagron   | Oxybutynin hydrochloride | 14A29-B09-293841 | 21704 <sup>†</sup> | 15      |
| Fagron   | Oxybutynin hydrochloride | 16A18-B02-321181 | 23268              | 40      |

- 146 574 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 19 spectra from 7 *Apo-Ident* customers from 12 batches from the substance/substance group *Oxybutynin hydrochloride*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance                | Batch            | Spectra |
|----------|--------------------------|------------------|---------|
| Fagron   | Oxybutynin hydrochloride | 13H26-B03        | 1       |
| Fagron   | Oxybutynin hydrochloride | 14/16-B03-300207 | 2       |
| Caelo    | Oxybutynin hydrochloride | 129099           | 1       |
| Fagron   | Oxybutynin hydrochloride | 127979           | 1       |
| Fagron   | Oxybutynin hydrochloride | 14A29-B09-307322 | 5       |
| Fagron   | Oxybutynin hydrochloride | 14a29-b09-307322 | 1       |
| Fagron   | Oxybutynin hydrochloride | 14I16-B03-300207 | 1       |
| Fagron   | Oxybutynin hydrochloride | 15F05-b03-315220 | 1       |
| Fagron   | Oxybutynin hydrochloride | 16A18-B02        | 1       |
| Fagron   | Oxybutynin hydrochloride | 15F05-B03-315221 | 2       |
| Fagron   | Oxybutynin hydrochloride | 16A18-B02-322538 | 2       |
| Fagron   | Oxybutynin hydrochloride | 16I23-B03-328916 | 1       |

- 69 614 spectra from 414 *Apo-Ident* customers from a total of 23 789 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Oxybutynin hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Oxybutynin hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 110           | 0              | 71 276        |
| <b>Type B</b> | 0              | 155           | 0              | 146 574       |
| <b>Type C</b> | 0              | 15            | 4              | 69 614        |

The substance/substance group *Oxybutynin hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.5455 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.1290 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested

reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21543     | 21543               | 0.00                         | 36.95                           |
| 21704     | 21543               | 3.43                         | 36.77                           |
| 22732     | 21543               | 2.66                         | 38.15                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | Oxytetracycline hydrochloride                                   |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20090-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Oxytetracycline hydrochloride; Oxytetracyclini hydrochloridum; Oxytetracyclinum hydrochloricum

### Special notes

When selecting the *Oxytetracycline hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Oxytetracycline hydrochloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Caelo    | Oxytetracycline ... | 12130001   | 20847     | 40      | 20120530    |
| Fagron   | Oxytetracycline ... | 13D08-N11  | 20848     | 60      | 20110131    |
| Caelo    | Oxytetracycline ... | 12328103   | 21039     | 40      | 20121214    |
| Euro OTC | Oxytetracycline ... | 1306022-02 | 21600     | 40      | 1507542     |
| Euro OTC | Oxytetracycline ... | 1506037    | 21836     | 40      | 20150721*   |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Oxytetracycline ... | 15D29-B99-309066 | 21915     | 40      | 20150522           |
| Euro OTC | Oxytetracycline ... | 1506037          | 21999     | 40      | 20150721*          |
| Caelo    | Oxytetracycline ... | 16077002         | 22503     | 40      | AR-16-FG-011460-01 |
| Euro OTC | Oxytetracycline ... | 1602025          | 22546     | 40      | 20160609*          |
| Euro OTC | Oxytetracycline ... | 1602025-01       | 22658     | 40      | AR-16-FG-014422-01 |
| Euro OTC | Oxytetracycline ... | 1602025          | 22669     | 40      | 20160609*          |
| Euro OTC | Oxytetracycline ... | 1602025-02       | 22839     | 40      | 20161021           |
| Euro OTC | Oxytetracycline ... | 1701034          | 23137     | 40      | 20170314*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 540 spectra of 13 reference samples from the substance/substance group *Oxytetracycline hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 70 846 spectra from a total of 1541 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 8 reference samples from the substance/substance group *Oxytetracycline hydrochloride*.

| Supplier | Substance                     | Batch            | Sample ID          | Spectra |
|----------|-------------------------------|------------------|--------------------|---------|
| Caelo    | Oxytetracycline hydrochloride | 12130001         | 20847 <sup>†</sup> | 20      |
| Euro OTC | Oxytetracycline hydrochloride | 1306022-02       | 21600 <sup>†</sup> | 20      |
| Euro OTC | Oxytetracycline hydrochloride | 1506037          | 21836 <sup>†</sup> | 20      |
| Fagron   | Oxytetracycline hydrochloride | 15D29-B99-309066 | 21915 <sup>†</sup> | 20      |
| Euro OTC | Oxytetracycline hydrochloride | 1506037          | 21999 <sup>†</sup> | 20      |
| Euro OTC | Oxytetracycline hydrochloride | 1602025-02       | 22846              | 40      |
| Fagron   | Oxytetracycline hydrochloride | 15L16-B02-322908 | 23226              | 40      |
| Fagron   | Oxytetracycline hydrochloride | 15L16-B02-322908 | 23417              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 146 509 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 344 spectra from 122 *Apo-Ident* customers from 85 batches from the substance/substance group *Oxytetracycline hydrochloride*.

| Supplier           | Substance                     | Batch            | Spectra |
|--------------------|-------------------------------|------------------|---------|
| Fagron             | Oxytetracycline hydrochloride | 912A-02865       | 1       |
| Caelo              | Oxytetracycline hydrochloride | 5041402          | 1       |
| Caelo              | Oxytetracycline hydrochloride | 12328103         | 2       |
| Caelo              | Oxytetracycline hydrochloride | 12091405         | 1       |
| Euro OTC           | Oxytetracycline hydrochloride | 1205028-02       | 14      |
| Euro OTC           | Oxytetracycline hydrochloride | 1205028          | 1       |
| Caelo              | Oxytetracycline hydrochloride | 12328107         | 1       |
| Fagron             | Oxytetracycline hydrochloride | 12G10-N04        | 10      |
| Euro OTC           | Oxytetracycline hydrochloride | 1306022-01       | 25      |
| Euro OTC           | Oxytetracycline hydrochloride | 1306022          | 1       |
| Euro OTC           | Oxytetracycline hydrochloride | 1306022-02       | 20      |
| Euro OTC           | Oxytetracycline hydrochloride | 1306022-03       | 6       |
| Fagron             | Oxytetracycline hydrochloride | 130602203        | 1       |
| Fagron             | Oxytetracycline hydrochloride | 13I26-N11        | 1       |
| Fagron             | Oxytetracycline hydrochloride | 13L19-B33        | 4       |
| Caelo              | Oxytetracycline hydrochloride | 13L19-B33        | 1       |
| Caelo              | Oxytetracycline hydrochloride | 13L19-B33-290730 | 1       |
| Fagron             | Oxytetracycline hydrochloride | 13L19-B33-290730 | 3       |
| Fagron             | Oxytetracycline hydrochloride | 13L19-B33-290731 | 3       |
| Fagropn            | Oxytetracycline hydrochloride | 13L19-B33-290731 | 1       |
| Fagron             | Oxytetracycline hydrochloride |                  | 1       |
| Fagron             | Oxytetracycline hydrochloride | 13L19-B33-290732 | 1       |
| Fagron             | Oxytetracycline hydrochloride | 14/22-B01-301465 | 2       |
| Euro OTC           | Oxytetracycline hydrochloride | 1407011202       | 1       |
| Euro OTC           | Oxytetracycline hydrochloride | 14070120-02      | 1       |
| Euro OTC           | Oxytetracycline hydrochloride | 1407012-01       | 11      |
| Euro OTC           | Oxytetracycline hydrochloride | 1407012-02       | 11      |
| Phönix Gotha       | Oxytetracycline hydrochloride | 1407012-02       | 1       |
| Norbrook/Gehe      | Oxytetracycline hydrochloride | 140701203        | 1       |
| Euro OTC           | Oxytetracycline hydrochloride | 1407012-03       | 3       |
| Euro OTC           | Oxytetracycline hydrochloride | 14128003         | 2       |
| Caelo              | Oxytetracycline hydrochloride | 14128003         | 1       |
| Euro OTC           | Oxytetracycline hydrochloride | 15051507         | 1       |
| Caelo              | Oxytetracycline hydrochloride | 14128004         | 1       |
| Caelo              | Oxytetracycline hydrochloride | 15060108         | 1       |
| Fagron             | Oxytetracycline hydrochloride | 14I22-B01        | 1       |
| Caelo              | Oxytetracycline hydrochloride | 15060109         | 5       |
| Fagron             | Oxytetracycline hydrochloride | 14I22-B01-301465 | 1       |
| Caesar&Loretz GmbH | Oxytetracycline hydrochloride | 15060109         | 1       |
| Fagro/Anzag        | Oxytetracycline hydrochloride | 14I22-B01-301464 | 1       |
| Fagron             | Oxytetracycline hydrochloride | 14I22-B01-301464 | 1       |
| Euro OTC           | Oxytetracycline hydrochloride | 1506037          | 2       |

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| Supplier                   | Substance                     | Batch            | Spectra |
|----------------------------|-------------------------------|------------------|---------|
| Caelo                      | Oxytetracycline hydrochloride | 1506037          | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 150603701        | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1506037-01       | 16      |
| Caelo                      | Oxytetracycline hydrochloride | 1506037-01       | 3       |
| Norbrook Lab.Ltd.          | Oxytetracycline hydrochloride | 1506037-01       | 2       |
| Laborchemie Apolda/Phönix  | Oxytetracycline hydrochloride | 1506037-02       | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1506037-02       | 20      |
| Caelo                      | Oxytetracycline hydrochloride | 1506037-02       | 1       |
| Caelo                      | Oxytetracycline hydrochloride | 150603702        | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1506037-03       | 11      |
| Euro OTC                   | Oxytetracycline hydrochloride | 150603703        | 1       |
| Fagron                     | Oxytetracycline hydrochloride | 15L16-B02-322908 | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1602025-01       | 14      |
| Fagron                     | Oxytetracycline hydrochloride | 15116-b02-322907 | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 15060377-01      | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1602025          | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1602025-02       | 7       |
| Euro OTC                   | Oxytetracycline hydrochloride | 160202501        | 1       |
| Caelo                      | Oxytetracycline hydrochloride | 1602025-02       | 2       |
| Gehe                       | Oxytetracycline hydrochloride | 1602025-02       | 2       |
| Caelo                      | Oxytetracycline hydrochloride | 16077001         | 2       |
| Caelo                      | Oxytetracycline hydrochloride | 16077002         | 1       |
| Caelo                      | Oxytetracycline hydrochloride | 16077003         | 2       |
| Caelo                      | Oxytetracycline hydrochloride | 16077007         | 2       |
| Caelo                      | Oxytetracycline hydrochloride | 16077008         | 2       |
| Apomix/Kehr                | Oxytetracycline hydrochloride | 16077014         | 1       |
| Caelo                      | Oxytetracycline hydrochloride | 16077009         | 1       |
| Caelo                      | Oxytetracycline hydrochloride | 16077011         | 1       |
| Fagron                     | Oxytetracycline hydrochloride | 3-45703A         | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 28011505         | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1701034-01       | 3       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1011045-01       | 3       |
| Fagron                     | Oxytetracycline hydrochloride | 4-49732A-2       | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 513E-02865       | 1       |
| Spangropharm               | Oxytetracycline hydrochloride | 1111061-01       | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1111061-01       | 11      |
| EuRho                      | Oxytetracycline hydrochloride | 1111061-01       | 1       |
| Gehe                       | Oxytetracycline hydrochloride | 11336507         | 1       |
| Caelo                      | Oxytetracycline hydrochloride | 11336509         | 1       |
| Caelo                      | Oxytetracycline hydrochloride | 11336507         | 1       |
| Caelo                      | Oxytetracycline hydrochloride | 11336510         | 6       |
| Gehe                       | Oxytetracycline hydrochloride | 11336509         | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1111061-61       | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 12050-28         | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 1205028-01       | 9       |
| phönix, 24.01.2013         | Oxytetracycline hydrochloride | 1205028-01       | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 120502801        | 1       |
| Phönix                     | Oxytetracycline hydrochloride | 1205028-01       | 1       |
| EuRho                      | Oxytetracycline hydrochloride | 1205028-01       | 2       |
| Alliance Healthcare        | Oxytetracycline hydrochloride | 1205028-02       | 1       |
| Euro OTC                   | Oxytetracycline hydrochloride | 120502802        | 2       |
| Alliance Healthcare        | Oxytetracycline hydrochloride | 1205222-01       | 1       |
| Caelo                      | Oxytetracycline hydrochloride | 12130001         | 3       |
| Anzag                      | Oxytetracycline hydrochloride | 12328103         | 1       |
| Caesar & Loretz GmbH Hi... | Oxytetracycline hydrochloride | 12328104         | 1       |
| Caelo                      | Oxytetracycline hydrochloride | 12328104         | 1       |
| Fagron                     | Oxytetracycline hydrochloride | 12A26-N05        | 6       |
| Phönix Gotha               | Oxytetracycline hydrochloride | 1232814          | 1       |
| Gehe                       | Oxytetracycline hydrochloride | 12A26-N05        | 2       |
| Caelo                      | Oxytetracycline hydrochloride | 12G10-N04        | 3       |

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| Supplier | Substance                     | Batch           | Spectra |
|----------|-------------------------------|-----------------|---------|
| Gehe     | Oxytetracycline hydrochloride | 12g10-n04       | 1       |
| Caelo    | Oxytetracycline hydrochloride | 1306022-01      | 1       |
| Fagron   | Oxytetracycline hydrochloride | 13D08-N11       | 10      |
| Caelo    | Oxytetracycline hydrochloride | 13D08-N11       | 1       |
| Caelo    | Oxytetracycline hydrochloride | 1407012-01      | 1       |
| Fagron   | Oxytetracycline hydrochloride | 13L19-B33-29073 | 1       |
| Caelo    | Oxytetracycline hydrochloride | 21021305        | 1       |
| Caelo    | Oxytetracycline hydrochloride | 2-28230A        | 1       |
| Euro OTC | Oxytetracycline hydrochloride | 700116          | 1       |
| Fagron   | Oxytetracycline hydrochloride | C22H25CIN209    | 1       |
|          | Oxytetracycline hydrochloride |                 | 1       |
| Gehe     | Oxytetracycline hydrochloride | 1205028-01      | 1       |
| Gehe     | Oxytetracycline hydrochloride | 1205028-02      | 2       |
| Gehe     | Oxytetracycline hydrochloride | 1306022-02      | 1       |

- 69 289 spectra from 414 *Apo-Ident* customers from a total of 23 720 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Oxytetracycline hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Oxytetracycline hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 540           | 0              | 70 846        |
| <b>Type B</b> | 0              | 220           | 0              | 146 509       |
| <b>Type C</b> | 0              | 331           | 13             | 69 289        |

The substance/substance group *Oxytetracycline hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.8889 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.2727 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 96.2209 % (> 95.3488 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20847     | 21999               | 6.96                         | 35.15                           |
| 20848     | 22503               | 12.05                        | 34.40                           |
| 21039     | 21600               | 6.92                         | 37.94                           |
| 21600     | 21600               | 0.00                         | 38.59                           |
| 21836     | 21836               | 0.00                         | 33.57                           |
| 21915     | 21836               | 15.74                        | 34.64                           |
| 21999     | 21999               | 0.00                         | 36.79                           |
| 22503     | 22503               | 0.00                         | 35.99                           |
| 22546     | 22546               | 0.00                         | 33.09                           |
| 22658     | 22658               | 0.00                         | 31.54                           |
| 22669     | 22669               | 0.00                         | 33.19                           |
| 22839     | 22503               | 10.93                        | 35.15                           |
| 23137     | 23137               | 0.00                         | 31.39                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Pancreas powder**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20976-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Pancreas powder; Pancreatinum; Pancreatis pulvis

### Special notes

When selecting the *Pancreas powder* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Pancreas powder*:

| Supplier | Substance       | Batch    | Sample ID | Spectra | Certificate |
|----------|-----------------|----------|-----------|---------|-------------|
| Caelo    | Pancreas powder | 13118902 | 20976     | 40      | 1402190     |
| Caelo    | Pancreas powder | 13395203 | 21481     | 40      | 20131218    |
| Caelo    | Pancreas powder | 161397   | 22482     | 40      | 20160527*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Pancreas powder*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 3 reference samples from the substance/substance group *Pancreas powder*.

| Supplier | Substance       | Batch    | Sample ID          | Spectra |
|----------|-----------------|----------|--------------------|---------|
| Caelo    | Pancreas powder | 10327501 | 20234              | 40      |
| Caelo    | Pancreas powder | 13395203 | 21481 <sup>†</sup> | 20      |
| Caelo    | Pancreas powder | 161397   | 22482 <sup>†</sup> | 20      |

- 146 649 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Pancreas powder*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Pancreas powder* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Pancreas powder* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Pancreas powder* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20976     | 20976               | 0.00                         | 24.14                           |
| 21481     | 20976               | 13.78                        | 27.66                           |
| 22482     | 22482               | 0.00                         | 27.36                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Papaverine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20481-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Papaverine hydrochloride; Papaverini hydrochloridum; Papaverinum hydrochloricum

### Special notes

When selecting the *Papaverine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Papaverine hydrochloride*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Papaverine hydro... | 13324310 | 21735     | 40      | 20130920    |
| Caelo    | Papaverine hydro... | 123161   | 23054     | 40      | 20121127*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Papaverine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Papaverine hydrochloride*.

| Supplier | Substance                | Batch     | Sample ID          | Spectra |
|----------|--------------------------|-----------|--------------------|---------|
| Caelo    | Papaverine hydrochloride | 9157221   | 20227              | 40      |
| Fagron   | Papaverine hydrochloride | 11L05-N10 | 20481              | 40      |
| Caelo    | Papaverine hydrochloride | 13324310  | 21735 <sup>†</sup> | 20      |
| Caelo    | Papaverine hydrochloride | 163159    | 23053              | 40      |

- 146 589 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 11 spectra from 9 *Apo-Ident* customers from 10 batches from the substance/substance group *Papaverine hydrochloride*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier            | Substance                | Batch         | Spectra |
|---------------------|--------------------------|---------------|---------|
| Phönix Gotha        | Papaverine hydrochloride | 13324306      | 1       |
| Caelo               | Papaverine hydrochloride | 12316105      | 1       |
| Caelo               | Papaverine hydrochloride | 15160608      | 2       |
| GATT-KOLLER/PHOENIX | Papaverine hydrochloride | 2927/07131314 | 1       |
| Phönix Gotha        | Papaverine hydrochloride | 12166101      | 1       |
| Phönix Gotha        | Papaverine hydrochloride | 9157221       | 1       |
| Caelo               | Papaverine hydrochloride | 13324307      | 1       |
| Caelo               | Papaverine hydrochloride | 12166112      | 1       |
| Caelo               | Papaverine hydrochloride | 91964419      | 1       |
| Caelo               | Papaverine hydrochloride |               | 1       |

- 69 622 spectra from 414 *Apo-Ident* customers from a total of 23 791 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Papaverine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Papaverine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 140           | 0              | 146 589       |
| <b>Type C</b> | 0              | 9             | 2              | 69 622        |

The substance/substance group *Papaverine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.7143 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21735     | 23054               | 11.76                        | 46.52                           |
| 23054     | 23054               | 0.00                         | 39.71                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Paracetamol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20972-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Paracetamol; Paracetamolum

### Special notes

When selecting the *Paracetamol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Paracetamol*:

| Supplier | Substance   | Batch      | Sample ID | Spectra | Certificate |
|----------|-------------|------------|-----------|---------|-------------|
| Fagron   | Paracetamol | 13D30-N03  | 20972     | 40      | 1402271     |
| Fagron   | Paracetamol | 13D16-N08  | 20973     | 40      | 1402296     |
| Fagron   | Paracetamol | 13G23-N03  | 20974     | 40      | 1402297     |
| Euro OTC | Paracetamol | 1111024-02 | 21598     | 40      | 20120123    |
| Caelo    | Paracetamol | 15075706   | 22608     | 40      | 20150424    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Paracetamol*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *Paracetamol*.

| Supplier    | Substance   | Batch      | Sample ID          | Spectra |
|-------------|-------------|------------|--------------------|---------|
| zu erfassen | Paracetamol | pending    | 20160              | 40      |
| Euro OTC    | Paracetamol | 1111024-02 | 21598 <sup>†</sup> | 20      |
| Caelo       | Paracetamol | 15075707   | 22822              | 40      |

- 146 629 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 37 spectra from 16 *Apo-Ident* customers from 25 batches from the substance/substance group *Paracetamol*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier             | Substance   | Batch        | Spectra |
|----------------------|-------------|--------------|---------|
| Caelo                | Paracetamol | 10325020     | 1       |
| Caelo                | Paracetamol | 11300120     | 4       |
| Caelo                | Paracetamol | 12G23-N04    | 1       |
| Caelo                | Paracetamol | 13082005     | 1       |
| Caelo                | Paracetamol | 13082008     | 1       |
| Caelo                | Paracetamol | 13082010     | 3       |
| Caelo                | Paracetamol | 13082011     | 1       |
| Caelo                | Paracetamol | 15075704     | 5       |
| Caelo                | Paracetamol | 13B05-N04    | 1       |
| Caelo                | Paracetamol | 15075708     | 1       |
| Caelo                | Paracetamol | 15217704     | 1       |
| Caesar & Loretz GmbH | Paracetamol | 15245901     | 1       |
| Caelo                | Paracetamol | 15245901     | 1       |
| Jenne                | Paracetamol | 15245901     | 1       |
| Caelo                | Paracetamol | 15245902     | 1       |
| Caelo                | Paracetamol | 1814U-02045  | 1       |
| Caelo                | Paracetamol | 1912M-02045  | 1       |
| Caelo                | Paracetamol | 2815I-02045  | 1       |
| Caelo                | Paracetamol | 10065102     | 1       |
| Caelo                | Paracetamol | 10325017     | 1       |
| Caelo                | Paracetamol | 10325018     | 1       |
| Caelo                | Paracetamol | 11300108     | 1       |
| Euro OTC             | Paracetamol | 1111024-02   | 1       |
| Euro OTC             | Paracetamol | 1111024-01   | 1       |
| Caelo                | Paracetamol | 11300113     | 2       |
| Caelo                | Paracetamol | Paracetamol1 | 1       |
| Caelo                | Paracetamol | Paracetamol2 | 1       |

- 69 596 spectra from 414 *Apo-Ident* customers from a total of 23 776 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Paracetamol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Paracetamol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 86            | 14             | 146 629       |
| <b>Type C</b> | 0              | 30            | 7              | 69 596        |

The substance/substance group *Paracetamol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 86.0000 % (> 83.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 81.0811 % (> 72.9730 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20972     | 20972               | 0.00                         | 59.46                           |
| 20973     | 20973               | 0.00                         | 59.89                           |
| 20974     | 20974               | 0.00                         | 61.07                           |
| 21598     | 20972               | 2.07                         | 59.57                           |
| 22608     | 20972               | 16.05                        | 51.89                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Patent blue V, E131**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20469-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Patent blue V, E131

### Special notes

When selecting the *Patent blue V, E131* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Patent blue V, E131*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Patent blue V, E... | 12364206 | 21384     | 40      | 1508043     |
| Caelo    | Patent blue V, E... | 12364206 | 21385     | 40      | 20130110    |
| Caelo    | Patent blue V, E... | 13351803 | 21695     | 40      | 20131114    |
| Caelo    | Patent blue V, E... | 13351807 | 22387     | 40      | 1702362     |
| Caelo    | Patent blue V, E... | 16306902 | 23215     | 40      | 20161220    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Patent blue V, E131*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Patent blue V, E131*.

| Supplier | Substance           | Batch    | Sample ID          | Spectra |
|----------|---------------------|----------|--------------------|---------|
| Caelo    | Patent blue V, E131 | 10379902 | 20209              | 40      |
| Caelo    | Patent blue V, E131 | 11138401 | 20469              | 40      |
| Caelo    | Patent blue V, E131 | 13351803 | 21695 <sup>†</sup> | 20      |
| Caelo    | Patent blue V, E131 | 16306902 | 23214              | 40      |

- 146 589 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 20 spectra from 18 *Apo-Ident* customers from 12 batches from the substance/substance group *Patent blue V, E131*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance           | Batch    | Spectra |
|----------|---------------------|----------|---------|
| Caelo    | Patent blue V, E131 | 11305303 | 3       |
| Caelo    | Patent blue V, E131 | 12364206 | 4       |
| Caelo    | Patent blue V, E131 | 13351807 | 3       |
| Caelo    | Patent blue V, E131 | 13351808 | 2       |
| Noweda   | Patent blue V, E131 | 10273001 | 1       |
| Caelo    | Patent blue V, E131 | 15060204 | 1       |
| Noweda   | Patent blue V, E131 | 11138402 | 1       |
| Caelo    | Patent blue V, E131 | 11305302 | 1       |
| Caelo    | Patent blue V, E131 | 12364202 | 1       |
| Caelo    | Patent blue V, E131 | 12364204 | 1       |
| Caelo    | Patent blue V, E131 | 13351803 | 1       |
| Caelo    | Patent blue V, E131 |          | 1       |

- 69 613 spectra from 414 *Apo-Ident* customers from a total of 23 789 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Patent blue V, E131* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Patent blue V, E131* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 140           | 0              | 146 589       |
| <b>Type C</b> | 0              | 19            | 1              | 69 613        |

The substance/substance group *Patent blue V, E131* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.7143 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 95.0000 % (> 80.0000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested

reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21384     | 21384               | 0.00                         | 106.97                          |
| 21385     | 21384               | 1.18                         | 106.33                          |
| 21695     | 22387               | 21.27                        | 105.54                          |
| 22387     | 22387               | 0.00                         | 104.25                          |
| 23215     | 21384               | 24.89                        | 99.33                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Phenazone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22532-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Phenazone; Phenazonum; Phenylidimethylpyrazolonum

### Special notes

When selecting the *Phenazone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Phenazone*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------|------------------|-----------|---------|--------------------|
| Fagron   | Phenazone | 13G16-B07-287172 | 22532     | 40      | AR-16-FG-011360-01 |
| Caelo    | Phenazone | 15415107         | 22827     | 40      | 20151215           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Phenazone*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 3 reference samples from the substance/substance group *Phenazone*.

| Supplier | Substance | Batch            | Sample ID | Spectra |
|----------|-----------|------------------|-----------|---------|
| Caelo    | Phenazone | 15415101         | 22576     | 40      |
| Fagron   | Phenazone | 13G16-B07-287172 | 22720     | 40      |
| Caelo    | Phenazone | 170836           | 23302     | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Phenazone*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Phenazone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Phenazone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 120           | 0              | 146 609       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Phenazone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22532     | 22532               | 0.00                         | 41.71                           |
| 22827     | 22532               | 8.42                         | 36.15                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Pheniramine maleate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20694-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Pheniramine maleate; Pheniramini maleas; Pheniraminum maleicum

### Special notes

When selecting the *Pheniramine maleate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Pheniramine maleate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Caelo    | Pheniramine male... | 12200502   | 20694     | 40      | 1401559     |
| Euro OTC | Pheniramine male... | 1109013-02 | 20756     | 40      | 20111122    |
| Fagron   | Pheniramine male... | 13D24-N04  | 20928     | 40      | 20130530    |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Pheniramine maleate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *Pheniramine maleate*.

| Supplier | Substance           | Batch    | Sample ID | Spectra |
|----------|---------------------|----------|-----------|---------|
| Caelo    | Pheniramine maleate | 15172702 | 22790     | 40      |
| Euro OTC | Pheniramine maleate | 1701021  | 23384     | 40      |

- 146 649 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 19 spectra from 13 *Apo-Ident* customers from 15 batches from the substance/substance group *Pheniramine maleate*.

| Supplier                   | Substance           | Batch            | Spectra |
|----------------------------|---------------------|------------------|---------|
| Caelo                      | Pheniramine maleate | 14C25-B01-302272 | 1       |
| Fagron                     | Pheniramine maleate | 14C25-B01-295293 | 3       |
| Euro OTC                   | Pheniramine maleate | 1209032-01       | 2       |
| Caelo                      | Pheniramine maleate | 12352602         | 1       |
| Cealo                      | Pheniramine maleate | 12352608         | 1       |
| Supriya LifeScience Ltd... | Pheniramine maleate | 14C25-B01        | 1       |

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| Supplier                   | Substance           | Batch            | Spectra |
|----------------------------|---------------------|------------------|---------|
| Euro OTC                   | Pheniramine maleate | 1411044-02       | 1       |
| Caelo                      | Pheniramine maleate | 14C25-B01-292540 | 1       |
| Caelo                      | Pheniramine maleate | 12352604         | 1       |
| Fagron                     | Pheniramine maleate | 14c25b01307150   | 1       |
| Supriya LifeScience Ltd... | Pheniramine maleate | SLL/P/1213063    | 1       |
| Fagron                     | Pheniramine maleate | 12I06-N02        | 1       |
| Alliance Healthcare        | Pheniramine maleate | 12L04-N05        | 1       |
| Fagron                     | Pheniramine maleate | 12L04-N05        | 1       |
| Caelo                      | Pheniramine maleate | 9276210          | 1       |
| Fagron                     | Pheniramine maleate | 32/06-N02        | 1       |

- 69 614 spectra from 414 *Apo-Ident* customers from a total of 23 786 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Pheniramine maleate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Pheniramine maleate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 16            | 3              | 69 614        |

The substance/substance group *Pheniramine maleate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the [Mahalanobis distance](#) to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20694     | 20694               | 0.00                         | 53.27                           |
| 20756     | 20694               | 16.83                        | 54.58                           |
| 20928     | 20694               | 7.53                         | 51.01                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Phenylbutazon**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20447-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Phenylbutazon; Phenylbutazonum

### Special notes

When selecting the *Phenylbutazon* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Phenylbutazon*:

| Supplier | Substance     | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------|------------|-----------|---------|--------------------|
| Caelo    | Phenylbutazon | 14057202   | 21379     | 40      | 20140321           |
| Euro OTC | Phenylbutazon | 1305050-02 | 21605     | 40      | AR-15-FG-005687-01 |
| Euro OTC | Phenylbutazon | 1507023    | 21855     | 40      | 20150805*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Phenylbutazon*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Phenylbutazon*.

| Supplier | Substance     | Batch      | Sample ID          | Spectra |
|----------|---------------|------------|--------------------|---------|
| Caelo    | Phenylbutazon | 102629010  | 20447              | 40      |
| Euro OTC | Phenylbutazon | 1305050-02 | 21605 <sup>†</sup> | 20      |
| Euro OTC | Phenylbutazon | 1507023    | 21855 <sup>†</sup> | 20      |
| Caelo    | Phenylbutazon | 161121     | 22471              | 60      |
| Euro OTC | Phenylbutazon | 1604033    | 22563              | 40      |

- 146 549 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 2 spectra from 2 *Apo-Ident* customers from 2 batches from the substance/substance group *Phenylbutazon*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance     | Batch     | Spectra |
|----------|---------------|-----------|---------|
| Caelo    | Phenylbutazon | 10262901  | 1       |
| Fagron   | Phenylbutazon | 11H26-N02 | 1       |

- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Phenylbutazon* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Phenylbutazon* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 180           | 0              | 146 549       |
| <b>Type C</b> | 0              | 2             | 0              | 69 631        |

The substance/substance group *Phenylbutazon* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.6667 %) |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21379     | 21855               | 3.92                         | 40.27                           |
| 21605     | 21605               | 0.00                         | 38.87                           |
| 21855     | 21855               | 0.00                         | 38.88                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Phenylephrine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20567-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Phenylephrine hydrochloride; Phenylephrini hydrochloridum; Phenylephrinum hydrochloricum

### Special notes

When selecting the *Phenylephrine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Phenylephrine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Phenylephrine hy... | 12J19-B40-288254 | 21051     | 40      | 20131210           |
| Fagron   | Phenylephrine hy... | 14H13-B02-308438 | 21960     | 40      | AR-16-FG-008920-01 |
| Fagron   | Phenylephrine hy... | 16A20-B07-317987 | 22388     | 40      | AR-16-FG-013385-01 |
| Euro OTC | Phenylephrine hy... | 1704009          | 23394     | 40      | 20170524*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Phenylephrine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Phenylephrine hydrochloride*.

| Supplier | Substance                   | Batch            | Sample ID          | Spectra |
|----------|-----------------------------|------------------|--------------------|---------|
| Fagron   | Phenylephrine hydrochloride | 11L22-N10        | 20567              | 40      |
| Fagron   | Phenylephrine hydrochloride | 11L22-N10        | 20594              | 40      |
| Fagron   | Phenylephrine hydrochloride | 14H13-B02-308438 | 21960 <sup>†</sup> | 20      |
| Fagron   | Phenylephrine hydrochloride | 17C23-B04-333878 | 23263              | 40      |
| Fagron   | Phenylephrine hydrochloride | 17C23-B04-333880 | 23267              | 40      |

- 146 549 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 36 spectra from 10 *Apo-Ident* customers from 23 batches from the substance/substance group *Phenylephrine hydrochloride*.

| Supplier | Substance                   | Batch            | Spectra |
|----------|-----------------------------|------------------|---------|
| Fagron   | Phenylephrine hydrochloride | 10091504         | 1       |
| Jenne    | Phenylephrine hydrochloride | 14H13-B02        | 2       |
| Fagron   | Phenylephrine hydrochloride | 12J19-B40-288253 | 2       |
| Fagron   | Phenylephrine hydrochloride | 13K25-B02-293844 | 3       |
| Fagron   | Phenylephrine hydrochloride | 14H13-B02-299814 | 1       |
| Fagron   | Phenylephrine hydrochloride | 14H13-B02-299816 | 3       |
| Phoenix  | Phenylephrine hydrochloride | 15F09-B08        | 1       |
| Fagron   | Phenylephrine hydrochloride | 14H13-B02-309892 | 3       |
| Fagron   | Phenylephrine hydrochloride | 12A03-N09        | 1       |
| Fagron   | Phenylephrine hydrochloride | 14H13B02299817   | 1       |
| Fagron   | Phenylephrine hydrochloride | 14H13B02-299817  | 1       |
| Fagron   | Phenylephrine hydrochloride | 12C08-N17        | 1       |
| Fagron   | Phenylephrine hydrochloride | 15F09-B08-316796 | 1       |
| Fagron   | Phenylephrine hydrochloride | 1021402          | 1       |
| Noweda   | Phenylephrine hydrochloride | 12F01-N20        | 2       |
| Fagron   | Phenylephrine hydrochloride | 12F01-N20        | 1       |
| Fagron   | Phenylephrine hydrochloride | 12g19-n04        | 1       |
| Fagron   | Phenylephrine hydrochloride | 12G19-N04        | 1       |
| Fagron   | Phenylephrine hydrochloride | 13A03-N09        | 4       |
| Fagron   | Phenylephrine hydrochloride | 13a03-n09        | 1       |
| Fagron   | Phenylephrine hydrochloride | 13D09-N02        | 1       |
| Fagron   | Phenylephrine hydrochloride | 13G10-N04        | 1       |
| Fagron   | Phenylephrine hydrochloride | 13B14-N03        | 1       |
| Fagron   | Phenylephrine hydrochloride | CH12F01-N20      | 1       |

- 69 597 spectra from 414 *Apo-Ident* customers from a total of 23 779 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Phenylephrine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Phenylephrine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 141           | 39             | 146 549       |
| <b>Type C</b> | 0              | 36            | 0              | 69 597        |

The substance/substance group *Phenylephrine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 78.3333 % (> 76.6667 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 83.3333 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21051     | 21960               | 2.22                         | 32.92                           |
| 21960     | 21960               | 0.00                         | 34.50                           |
| 22388     | 22388               | 0.00                         | 33.11                           |
| 23394     | 23394               | 0.00                         | 34.95                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Phenytoin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20949-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Phenytoin; Diphenylhydrantoinum; Phenytoinum

### Special notes

When selecting the *Phenytoin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Phenytoin*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Fagron   | Phenytoin | 13G26-N02        | 20949     | 40      | 1401380     |
| Fagron   | Phenytoin | 15E12-B05-312661 | 22271     | 30      | 20150519    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 70 spectra of 2 reference samples from the substance/substance group *Phenytoin*. These samples are listed above in the [calibration samples](#) section.
- 71 316 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 135 spectra of 4 reference samples from the substance/substance group *Phenytoin*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Fagron   | Phenytoin | 12I07-N02        | 20678              | 40      |
| Fagron   | Phenytoin | 15E12-B05-312661 | 22271 <sup>†</sup> | 15      |
| Fagron   | Phenytoin | 16C14-B06-325086 | 23110              | 40      |
| Fagron   | Phenytoin | 16C14-B06-325086 | 23377              | 40      |

- 146 594 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 3 spectra from 2 *Apo-Ident* customers from 3 batches from the substance/substance group *Phenytoin*.

| Supplier | Substance | Batch    | Spectra |
|----------|-----------|----------|---------|
| Fagron   | Phenytoin | 12C27N13 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

continued from previous page

| Supplier | Substance | Batch     | Spectra |
|----------|-----------|-----------|---------|
| Fagron   | Phenytoin | 12I07-N02 | 1       |
| Fagron   | Phenytoin | 13G26-N02 | 1       |

- 69 630 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Phenytoin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Phenytoin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 70            | 0              | 71 316        |
| <b>Type B</b> | 0              | 135           | 0              | 146 594       |
| <b>Type C</b> | 0              | 3             | 0              | 69 630        |

The substance/substance group *Phenytoin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 91.4286 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.5556 %) |
| <b>Type C</b> | 100.0000 % (> 99.8817 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20949     | 20949               | 0.00                         | 96.02                           |
| 22271     | 20949               | 6.03                         | 96.94                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Pilocarpine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21519-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Pilocarpine hydrochloride; Pilocarpini hydrochloridum; Pilocarpinum hydrochloricum

### Special notes

When selecting the *Pilocarpine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Pilocarpine hydrochloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Caelo    | Pilocarpine hydr... | 12217319   | 21519     | 40      | 1501660     |
| Euro OTC | Pilocarpine hydr... | 1305044-01 | 21629     | 40      | 20130725    |
| Euro OTC | Pilocarpine hydr... | 1603047    | 22553     | 40      | 20160429*   |
| Caelo    | Pilocarpine hydr... | 17124208   | 23371     | 40      | 20170607    |
| Euro OTC | Pilocarpine hydr... | 1305044-01 | 21629SI   | 40      | 20130725    |
| Euro OTC | Pilocarpine hydr... | 1603047    | 22553SI   | 40      | 20160429*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Pilocarpine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 420 spectra of 11 reference samples from the substance/substance group *Pilocarpine hydrochloride*.

| Supplier | Substance                 | Batch      | Sample ID            | Spectra |
|----------|---------------------------|------------|----------------------|---------|
| Caelo    | Pilocarpine hydrochloride | 9234907    | 20105                | 40      |
| Caelo    | Pilocarpine hydrochloride | 12217319   | 21518                | 60      |
| Caelo    | Pilocarpine hydrochloride | 12217319   | 21519 <sup>†</sup>   | 20      |
| Euro OTC | Pilocarpine hydrochloride | 1305044-01 | 21629 <sup>†</sup>   | 20      |
| Caelo    | Pilocarpine hydrochloride | 171595     | 23337                | 40      |
| Caelo    | Pilocarpine hydrochloride | 171242     | 23338                | 40      |
| Caelo    | Pilocarpine hydrochloride | 12217319   | 21518SI              | 60      |
| Euro OTC | Pilocarpine hydrochloride | 1305044-01 | 21629SI <sup>†</sup> | 20      |
| Caelo    | Pilocarpine hydrochloride | 171595     | 23337SI              | 40      |
| Caelo    | Pilocarpine hydrochloride | 171242     | 23338SI              | 40      |
| Caelo    | Pilocarpine hydrochloride | 17124208   | 23371SI              | 40      |

- 146 309 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 31 spectra from 26 *Apo-Ident* customers from 21 batches from the substance/substance group *Pilocarpine hydrochloride*.

| Supplier | Substance                 | Batch         | Spectra |
|----------|---------------------------|---------------|---------|
| Caelo    | Pilocarpine hydrochloride | 12217316      | 1       |
| Euro OTC | Pilocarpine hydrochloride | 13050-14-01   | 1       |
| Euro OTC | Pilocarpine hydrochloride | 1305044-01    | 5       |
| Euro OTC | Pilocarpine hydrochloride | 130504401     | 2       |
| Euro OTG | Pilocarpine hydrochloride | 1305044-01    | 1       |
| Caelo    | Pilocarpine hydrochloride | 1305044-03    | 1       |
| Euro OTC | Pilocarpine hydrochloride | 1305044-03    | 2       |
| Fagron   | Pilocarpine hydrochloride | 13H24-N03     | 1       |
| Gehe     | Pilocarpine hydrochloride | 15198610      | 1       |
| Leyhs    | Pilocarpine hydrochloride | 15198701      | 1       |
| Noweda   | Pilocarpine hydrochloride | 11037801      | 1       |
| Euro OTC | Pilocarpine hydrochloride | 1603047-01    | 1       |
| Euro OTC | Pilocarpine hydrochloride | 1202031-02    | 1       |
| Caelo    | Pilocarpine hydrochloride | 12217302      | 1       |
| Sanacorp | Pilocarpine hydrochloride | 12217302      | 1       |
| Noweda   | Pilocarpine hydrochloride | 10CD04        | 1       |
| Caelo    | Pilocarpine hydrochloride | 12217307      | 1       |
| Euro OTC | Pilocarpine hydrochloride | 1202031-01    | 1       |
| Caelo    | Pilocarpine hydrochloride | 12K07-N09     | 1       |
| Caelo    | Pilocarpine hydrochloride | 1116190       | 1       |
| Caelo    | Pilocarpine hydrochloride | 25051303      | 1       |
| Caelo    | Pilocarpine hydrochloride | 130504401     | 1       |
| Caelo    | Pilocarpine hydrochloride | 2211112032607 | 1       |
| Euro OTC | Pilocarpine hydrochloride | 2909041V-02   | 1       |
| Euro OTC | Pilocarpine hydrochloride | Euroo         | 1       |

- 69 602 spectra from 414 *Apo-Ident* customers from a total of 23 780 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Pilocarpine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Pilocarpine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 414           | 6              | 146 309       |
| <b>Type C</b> | 0              | 25            | 6              | 69 602        |

The substance/substance group *Pilocarpine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 98.5714 % (> 97.8571 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 80.6452 % (> 70.9677 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21519     | 21519               | 0.00                         | 36.68                           |
| 21629     | 21519               | 5.66                         | 38.45                           |
| 22553     | 22553               | 0.00                         | 35.80                           |
| 23371     | 21519               | 5.03                         | 39.48                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Poloxamers 407**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20540-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Poloxamers 407; Poloxamera

### Special notes

When selecting the *Poloxamers 407* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Poloxamers 407*:

| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate        |
|----------|----------------|------------------|-----------|---------|--------------------|
| Caelo    | Poloxamers 407 | 14196101         | 21652     | 40      | AR-14-FG-013090-01 |
| Fagron   | Poloxamers 407 | 14G17-B03-296866 | 21726     | 40      | 20140806           |
| Caelo    | Poloxamers 407 | 16242605         | 23257     | 40      | 20160915           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Poloxamers 407*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 6 reference samples from the substance/substance group *Poloxamers 407*.

| Supplier | Substance      | Batch            | Sample ID          | Spectra |
|----------|----------------|------------------|--------------------|---------|
| Caelo    | Poloxamers 407 | 12044205         | 20540              | 40      |
| Caelo    | Poloxamers 407 | 12044205         | 20568              | 40      |
| Caelo    | Poloxamers 407 | 12044202         | 20607              | 40      |
| Caelo    | Poloxamers 407 | 14196101         | 21652 <sup>†</sup> | 20      |
| Fagron   | Poloxamers 407 | 14G17-B03-296866 | 21726 <sup>†</sup> | 20      |
| Caelo    | Poloxamers 407 | 170486           | 23311              | 40      |

- 146 529 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 35 spectra from 25 *Apo-Ident* customers from 25 batches from the substance/substance group *Poloxamers 407*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier             | Substance      | Batch            | Spectra |
|----------------------|----------------|------------------|---------|
| Fagron               | Poloxamers 407 | 315E-07027       | 1       |
| Caelo                | Poloxamers 407 | 12286806         | 1       |
| Fagron               | Poloxamers 407 | 914I-07027       | 1       |
| Caelo                | Poloxamers 407 | 13133203         | 2       |
| Caelo                | Poloxamers 407 | 14196101         | 2       |
| Caelo                | Poloxamers 407 | 13133207         | 1       |
| Caelo                | Poloxamers 407 | 14196104         | 1       |
| Caelo                | Poloxamers 407 | 14196108         | 3       |
| Caelo                | Poloxamers 407 | 14196105         | 1       |
| Fagron               | Poloxamers 407 | 13G29-N01        | 1       |
| Caesar & Loretz GmbH | Poloxamers 407 | 15183102         | 1       |
| Caelo                | Poloxamers 407 | 14359501         | 1       |
| Caelo                | Poloxamers 407 | 15397802         | 5       |
| Caelo                | Poloxamers 407 | 16242601         | 1       |
| Fagron               | Poloxamers 407 | 15A26-B03-303503 | 1       |
| Fagron               | Poloxamers 407 | 5315I-07027      | 1       |
| Fagron               | Poloxamers 407 | WPW1610C         | 1       |
| Caelo                | Poloxamers 407 | 12286801         | 2       |
| Phonix               | Poloxamers 407 | 12/13-N10        | 1       |
| Caelo                | Poloxamers 407 | AKD16            | 1       |
| Caelo                | Poloxamers 407 | 12286805         | 1       |
| Caelo                | Poloxamers 407 | 13133201         | 1       |
| Fagron               | Poloxamers 407 | 12K23-N03        | 1       |
| Noweda               | Poloxamers 407 | 13133201         | 1       |
| Fagron               | Poloxamers 407 | 13G29-N01        | 1       |
| Fagron               | Poloxamers 407 | 5211Q-07027      | 1       |

- 69 598 spectra from 414 *Apo-Ident* customers from a total of 23 776 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Poloxamers 407* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Poloxamers 407* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 200           | 0              | 146 529       |
| <b>Type C</b> | 0              | 33            | 2              | 69 598        |

The substance/substance group *Poloxamers 407* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 94.2857 % (> 85.7143 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21652     | 21652               | 0.00                         | 47.05                           |
| 21726     | 21652               | 4.17                         | 44.89                           |
| 23257     | 21652               | 3.49                         | 48.93                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Polymyxin B sulfate</b>                                      |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20853-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Polymyxin B sulfate; Polymixinum-B-sulfuricum; Polymyxin B sulphate; Polymyxini B sulfas

### Special notes

When selecting the *Polymyxin B sulfate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Polymyxin B sulfate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Fagron   | Polymyxin B sulf... | 13C12-N02  | 20853     | 40      | 1402691     |
| Euro OTC | Polymyxin B sulf... | 1304033-01 | 21094     | 39      | 20130829    |
| Fagron   | Polymyxin B sulf... | 12G13-N05  | 21258     | 40      | 1410347     |
| Euro OTC | Polymyxin B sulf... | 1202039-02 | 21329     | 40      | 1411033     |
| Euro OTC | Polymyxin B sulf... | 1304033-02 | 21584     | 40      | 20130612    |

*continued on the next page*

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| Supplier | Substance             | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------------------|------------------|-----------|---------|--------------------|
| Fagron   | Polymyxin B sulf. ... | 13I13-N05        | 21595     | 40      | AR-15-FG-001516-01 |
| Fagron   | Polymyxin B sulf. ... | 14F04-B03-296722 | 21957     | 40      | 20140708           |
| Euro OTC | Polymyxin B sulf. ... | 1505005-01       | 21980     | 40      | AR-16-FG-005387-01 |
| Fagron   | Polymyxin B sulf. ... | 15H14-B01-314364 | 22323     | 40      | 20150902           |
| Caelo    | Polymyxin B sulf. ... | 153501           | 22451     | 40      | 20160318*          |
| Euro OTC | Polymyxin B sulf. ... | 1604016          | 22542     | 40      | 20160509*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 439 spectra of 11 reference samples from the substance/substance group *Polymyxin B sulfate*. These samples are listed above in the [calibration samples](#) section.
- 70 947 spectra from a total of 1541 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 281 spectra of 11 reference samples from the substance/substance group *Polymyxin B sulfate*.

| Supplier | Substance           | Batch            | Sample ID          | Spectra |
|----------|---------------------|------------------|--------------------|---------|
| Euro OTC | Polymyxin B sulfate | 1202039-02       | 20904              | 40      |
| Fagron   | Polymyxin B sulfate | 13E06-N12        | 20912              | 40      |
| Euro OTC | Polymyxin B sulfate | 1304033-01       | 21094 <sup>†</sup> | 1       |
| Euro OTC | Polymyxin B sulfate | 1304033-02       | 21584 <sup>†</sup> | 20      |
| Fagron   | Polymyxin B sulfate | 13I13-N05        | 21595 <sup>†</sup> | 20      |
| Fagron   | Polymyxin B sulfate | 14F04-B03-296722 | 21957 <sup>†</sup> | 20      |
| Euro OTC | Polymyxin B sulfate | 1505005-01       | 21980 <sup>†</sup> | 20      |
| Fagron   | Polymyxin B sulfate | 15H14-B01-314364 | 22323 <sup>†</sup> | 20      |
| Caelo    | Polymyxin B sulfate | 153501           | 22451 <sup>†</sup> | 20      |
| Euro OTC | Polymyxin B sulfate | 1701010          | 23012              | 40      |
| Euro OTC | Polymyxin B sulfate | 1707013          | 23554              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 448 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 54 spectra from 41 *Apo-Ident* customers from 33 batches from the substance/substance group *Polymyxin B sulfate*.

| Supplier            | Substance           | Batch            | Spectra |
|---------------------|---------------------|------------------|---------|
| Fagron              | Polymyxin B sulfate | 912A-03315       | 1       |
| Caelo               | Polymyxin B sulfate | 1102013-01       | 1       |
| Euro OTC            | Polymyxin B sulfate | 11091419         | 1       |
| Fagron              | Polymyxin B sulfate | 13/13-N05        | 1       |
| Fagron              | Polymyxin B sulfate | 12G13-N05        | 1       |
| Rondell Apotheke    | Polymyxin B sulfate | 121161           | 1       |
| Euro OTC            | Polymyxin B sulfate | 1304033-01       | 2       |
| Euro OTC            | Polymyxin B sulfate | 1304033-02       | 1       |
| Caelo               | Polymyxin B sulfate | 130403302        | 1       |
| Euroo/Phoenix       | Polymyxin B sulfate | 1304033-02       | 1       |
| Großhandel          | Polymyxin B sulfate | 1304033-02       | 1       |
| Caelo               | Polymyxin B sulfate | 1304033-03       | 1       |
| Euro OTC            | Polymyxin B sulfate | 1304033-03       | 1       |
| Euro OTC            | Polymyxin B sulfate | 130416           | 2       |
| Fagron              | Polymyxin B sulfate | 13G05-N06        | 2       |
| Caelo               | Polymyxin B sulfate | 13H28-B02-287953 | 1       |
| Fagron              | Polymyxin B sulfate | 13H28-B02-287954 | 1       |
| Euro OTC            | Polymyxin B sulfate | 1406012-01       | 3       |
| Euro OTC            | Polymyxin B sulfate | 140601202        | 2       |
| Euro OTC            | Polymyxin B sulfate | 1406012-02       | 1       |
| Fagron              | Polymyxin B sulfate | 14F04-B03-296721 | 1       |
| Euro OTC            | Polymyxin B sulfate | 1505005-01       | 4       |
| Euro OTC            | Polymyxin B sulfate | 150500501        | 1       |
| Caelo               | Polymyxin B sulfate | 1604016-01       | 1       |
| Fagron              | Polymyxin B sulfate | 16C01-B04        | 2       |
| Euro OTC            | Polymyxin B sulfate | 1604016-02       | 1       |
| Fagron              | Polymyxin B sulfate | 16C01-B04-322012 | 1       |
| Euro OTC            | Polymyxin B sulfate | 1701010-01       | 1       |
| Euro OTC            | Polymyxin B sulfate | 23051502         | 1       |
| Anzag               | Polymyxin B sulfate | 11K28-N07        | 1       |
| Euro OTC            | Polymyxin B sulfate | 1202039-01       | 1       |
| EuRho               | Polymyxin B sulfate | 1202039-01       | 1       |
| Phönix              | Polymyxin B sulfate | 1202039-01       | 1       |
| Alliance Healthcare | Polymyxin B sulfate | 1202039-02       | 1       |
| Euro OTC            | Polymyxin B sulfate | 1202039-02       | 4       |
| euroct/gehe         | Polymyxin B sulfate | 1202039-02       | 1       |
| Fagron              | Polymyxin B sulfate | 12D05-N01        | 1       |
| Fagron              | Polymyxin B sulfate | 12G25-N06        | 1       |
| phönix,24.01.2013   | Polymyxin B sulfate | 12D05-N01        | 1       |
| Euro OTC            | Polymyxin B sulfate | 25101201         | 1       |
| Fagron              | Polymyxin B sulfate | 13H28-B02-87953  | 1       |

- 69 579 spectra from 414 *Apo-Ident* customers from a total of 23 769 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Polymyxin B sulfate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Polymyxin B sulfate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 439           | 0              | 70 947        |
| Type B | 0              | 262           | 19             | 146 448       |
| Type C | 0              | 47            | 7              | 69 579        |

The substance/substance group *Polymyxin B sulfate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.6333 %) |
| Type B | 100.0000 % (> 99.9923 %) | 93.2384 % (> 92.1708 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 87.0370 % (> 81.4815 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20853     | 20853               | 0.00                         | 20.53                           |
| 21094     | 21980               | 2.66                         | 25.39                           |
| 21258     | 21258               | 0.00                         | 22.56                           |
| 21329     | 21329               | 0.00                         | 21.83                           |
| 21584     | 21980               | 3.66                         | 24.82                           |
| 21595     | 21595               | 0.00                         | 23.81                           |
| 21957     | 21329               | 12.15                        | 25.85                           |

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| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21980            | 21980                      | 0.00                                | 23.83                                  |
| 22323            | 21980                      | 7.00                                | 25.62                                  |
| 22451            | 22451                      | 0.00                                | 33.17                                  |
| 22542            | 22542                      | 0.00                                | 20.46                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Potassium citrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20021-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Potassium citrate; Kalii citras; Kalii citricum

### Special notes

When selecting the *Potassium citrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Potassium citrate*:

| Supplier | Substance         | Batch    | Sample ID | Spectra | Certificate |
|----------|-------------------|----------|-----------|---------|-------------|
| Caelo    | Potassium citrate | 11320212 | 20655     | 40      | 20111201    |
| Caelo    | Potassium citrate | 13317618 | 21452     | 40      | 20130926    |
| Caelo    | Potassium citrate | 15123103 | 21775     | 40      | 20150414    |
| Euro OTC | Potassium citrate | 1509044  | 21936     | 40      | 20151013*   |
| Caelo    | Potassium citrate | 161130   | 22476     | 40      | 20160602*   |
| Euro OTC | Potassium citrate | 1611017  | 22921     | 40      | 20161207*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Potassium citrate*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 381 spectra of 11 reference samples from the substance/substance group *Potassium citrate*.

| Supplier | Substance         | Batch      | Sample ID          | Spectra |
|----------|-------------------|------------|--------------------|---------|
| Caelo    | Potassium citrate | 83305269   | 20021              | 61      |
| Caelo    | Potassium citrate | 11102206   | 20502              | 40      |
| Euro OTC | Potassium citrate | 1204016-01 | 20575              | 40      |
| Caelo    | Potassium citrate | 13317618   | 21452 <sup>†</sup> | 20      |
| Caelo    | Potassium citrate | 15123103   | 21775 <sup>†</sup> | 20      |
| Euro OTC | Potassium citrate | 1509044    | 21936 <sup>†</sup> | 20      |
| Caelo    | Potassium citrate | 161130     | 22476 <sup>†</sup> | 20      |
| Euro OTC | Potassium citrate | 1603040    | 22521              | 40      |
| Euro OTC | Potassium citrate | 1606041    | 22676              | 40      |
| Caelo    | Potassium citrate | 170929     | 23290              | 40      |
| Euro OTC | Potassium citrate | 1705024    | 23428              | 40      |

- 146 348 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 290 spectra from 111 *Apo-Ident* customers from 111 batches from the substance/substance group *Potassium citrate*.

| Supplier           | Substance         | Batch          | Spectra |
|--------------------|-------------------|----------------|---------|
| Caelo              | Potassium citrate | 14138105       | 5       |
| Caelo              | Potassium citrate | 1603040-01     | 1       |
| Caelo              | Potassium citrate | 1215309        | 1       |
| Caelo              | Potassium citrate | 12299207       | 5       |
| Caelo              | Potassium citrate |                | 16      |
| Gutenberg-Apotheke | Potassium citrate | 13135907       | 1       |
| Caelo              | Potassium citrate | 13135907       | 4       |
| Caelo              | Potassium citrate | 11320202       | 2       |
| Caelo              | Potassium citrate | 1234           | 5       |
| Caelo              | Potassium citrate | 13080602       | 9       |
| Caelo              | Potassium citrate | 5021509        | 1       |
| Caelo              | Potassium citrate | 12299203       | 4       |
| Caelo              | Potassium citrate | 12334          | 1       |
| Labor              | Potassium citrate | 1234           | 2       |
| Testsubstanz       | Potassium citrate |                | 1       |
| Euro OTC           | Potassium citrate | 123456         | 6       |
| Caelo              | Potassium citrate | 12345678       | 2       |
| Caelo              | Potassium citrate | 123654879      | 1       |
| Caelo              | Potassium citrate | 123Test        | 3       |
| Caelo              | Potassium citrate | 123test        | 2       |
| Caelo              | Potassium citrate | 123Testmessung | 1       |
| Caelo              | Potassium citrate | 12456          | 1       |
| Caelo              | Potassium citrate | 12648          | 1       |
| Caelo              | Potassium citrate | 13080603       | 2       |
| Euro OTC           | Potassium citrate | 1311036-01     | 10      |
| Caelo              | Potassium citrate | 1311036-01     | 2       |
| EuRho/Phönix       | Potassium citrate | 1311036-01     | 1       |
| Caelo              | Potassium citrate | 13135902       | 1       |
| Caelo              | Potassium citrate | 13135908       | 2       |
| Phoenix            | Potassium citrate | 1326PLV-1739   | 1       |
| Caelo              | Potassium citrate | 13317602       | 5       |
| Caelo              | Potassium citrate | 13317603       | 4       |
| Caelo              | Potassium citrate | 13317604       | 2       |
| Caelo              | Potassium citrate | 13317613       | 3       |
| Phoenix Goettin    | Potassium citrate | 13317613       | 1       |
| Caelo              | Potassium citrate | 13317617       | 2       |
| Caelo              | Potassium citrate | 13317618       | 4       |
| Caelo              | Potassium citrate | 13317619       | 3       |
| Phoenix 08.07.2014 | Potassium citrate | 13317624       | 1       |
| Euro OTC           | Potassium citrate | 1406025-01     | 2       |
| Euro OTC           | Potassium citrate | 1410014-01     | 4       |
| Caelo              | Potassium citrate | 14138107       | 2       |
| Caelo              | Potassium citrate | 14138112       | 2       |
| Caelo              | Potassium citrate | 14138118       | 3       |
| Caelo              | Potassium citrate | 14138119       | 1       |
| Caelo              | Potassium citrate | 1413812        | 1       |
| Berkel AHK         | Potassium citrate | 1438105        | 1       |
| Euro OTC           | Potassium citrate | 1504024-01     | 3       |
| Euro OTC           | Potassium citrate | 1509044-01     | 3       |
| Caelo              | Potassium citrate | 15123102       | 2       |
| Caelo              | Potassium citrate | 15123103       | 2       |
| Phönix             | Potassium citrate | 15123103       | 1       |

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| <b>Supplier</b>   | <b>Substance</b>  | <b>Batch</b> | <b>Spectra</b> |
|-------------------|-------------------|--------------|----------------|
| Caelo             | Potassium citrate | 15148701     | 4              |
| Caelo             | Potassium citrate | 15148702     | 1              |
| Caelo             | Potassium citrate | 15148706     | 4              |
| Caelo             | Potassium citrate | 15148707     | 1              |
| Phoenix           | Potassium citrate | 15148708     | 1              |
| Caelo             | Potassium citrate | 15435701     | 2              |
| Caelo             | Potassium citrate | 15435709     | 1              |
| Caelo             | Potassium citrate | 15435710     | 1              |
| Caelo             | Potassium citrate | 1543702      | 1              |
| Caelo             | Potassium citrate | 154357025    | 1              |
| Euro OTC          | Potassium citrate | 1603040-01   | 12             |
| Euro OTC          | Potassium citrate | 160601-01    | 1              |
| Euro OTC          | Potassium citrate | 160604-01    | 1              |
| Euro OTC          | Potassium citrate | 1606041-01   | 4              |
| Euro OTC          | Potassium citrate | 1611017-01   | 1              |
| Caelo             | Potassium citrate | 16113002     | 1              |
| Caelo             | Potassium citrate | 16113003     | 1              |
| Caelo             | Potassium citrate | 17061402     | 1              |
| Caelo             | Potassium citrate | 189645       | 1              |
| Caelo             | Potassium citrate | 2114M1737    | 1              |
| Caelo             | Potassium citrate | 3012Q-01737  | 1              |
| Caelo             | Potassium citrate | 83305269     | 1              |
| Euro OTC          | Potassium citrate |              | 1              |
| Caelo             | Potassium citrate | 70913Kaci    | 1              |
| Caelo             | Potassium citrate | 9259120      | 1              |
| Caelo             | Potassium citrate | 9259107      | 1              |
| Caelo             | Potassium citrate | 10067413     | 1              |
| lohmann           | Potassium citrate | 1051470      | 1              |
| Caelo             | Potassium citrate | 11102201     | 1              |
| Klenk             | Potassium citrate | 11102219     | 1              |
| Caelo             | Potassium citrate | 1112008-01   | 1              |
| Caelo             | Potassium citrate | 11320203     | 2              |
| Caelo             | Potassium citrate | 11320201     | 1              |
| Caelo             | Potassium citrate | 11320212     | 5              |
| Caelo             | Potassium citrate | 11320213     | 2              |
| Euro OTC          | Potassium citrate | 1204016-01   | 6              |
| Sanacorp/ euRho   | Potassium citrate | 1204016-01   | 1              |
| Caelo             | Potassium citrate | 1204016-01   | 1              |
| Euro OTC          | Potassium citrate | 1209005-01   | 3              |
| Euro OTC          | Potassium citrate | 1211006-01   | 3              |
| Phönix            | Potassium citrate | 1211006-01   | 1              |
| Caelo             | Potassium citrate | 1213503      | 1              |
| Caelo             | Potassium citrate | 12135301     | 2              |
| Caelo             | Potassium citrate | 12135302     | 5              |
| phönix,10.12.12   | Potassium citrate | 12135302     | 1              |
| Caelo             | Potassium citrate | 12135303     | 2              |
| Erika apotheke    | Potassium citrate | 12135306     | 2              |
| Caelo             | Potassium citrate | 12135309     | 3              |
| Phönix            | Potassium citrate | 12135310     | 4              |
| Sanacorb          | Potassium citrate | 12135311     | 2              |
| Caelo             | Potassium citrate | 12135311     | 1              |
| Caelo             | Potassium citrate | 12299201     | 7              |
| Großhandel        | Potassium citrate | 12299201     | 1              |
| Caelo             | Potassium citrate | 12299202     | 2              |
| Hiperscan         | Potassium citrate |              | 1              |
| Fagron            | Potassium citrate | 1234         | 1              |
| Fagron            | Potassium citrate | 1234567      | 1              |
| EuRho             | Potassium citrate | 1306032-01   | 3              |
| Euro OTC          | Potassium citrate | 1306032-01   | 1              |
| Phönix 21.05.2013 | Potassium citrate | 13080602     | 1              |

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| Supplier  | Substance         | Batch        | Spectra |
|-----------|-------------------|--------------|---------|
| Caelo     | Potassium citrate | 13080604     | 1       |
| Gehe      | Potassium citrate | 1311036-01   | 1       |
| Caelo     | Potassium citrate | 13135903     | 3       |
| Caelo     | Potassium citrate | 13135904     | 3       |
| Caelo     | Potassium citrate | 1313598      | 1       |
| Euro OTC  | Potassium citrate | 22101303     | 1       |
| Caelo     | Potassium citrate | 23121-01737  | 1       |
| Caelo     | Potassium citrate | 3112M01737   | 1       |
| Caelo     | Potassium citrate | 33131-01737  | 1       |
| Caelo     | Potassium citrate | 28021402     | 1       |
| fragon    | Potassium citrate |              | 1       |
| ghfgh     | Potassium citrate | 3654645      | 1       |
| Caelo     | Potassium citrate | 3456         | 1       |
| Caelo     | Potassium citrate | 5555         | 1       |
| Caelo     | Potassium citrate | 411025-1-P   | 1       |
| Fagron    | Potassium citrate |              | 1       |
| Caelo     | Potassium citrate | 71730128     | 1       |
| Caelo     | Potassium citrate | 71730367     | 1       |
| Euro OTC  | Potassium citrate | Ch1209005-01 | 1       |
| Euro OTC  | Potassium citrate | Ch1304022-01 | 2       |
| HiperScan | Potassium citrate |              | 1       |

- 69 343 spectra from 414 *Apo-Ident* customers from a total of 23 699 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Potassium citrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Potassium citrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 381           | 0              | 146 348       |
| <b>Type C</b> | 0              | 289           | 1              | 69 343        |

The substance/substance group *Potassium citrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.4252 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 99.6552 % (> 98.6207 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20655     | 21936               | 4.23                         | 49.73                           |
| 21452     | 22476               | 5.62                         | 49.29                           |
| 21775     | 21936               | 3.67                         | 49.59                           |
| 21936     | 21936               | 0.00                         | 50.00                           |
| 22476     | 22476               | 0.00                         | 49.73                           |
| 22921     | 22921               | 0.00                         | 49.74                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Potassium hydrogen tartrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20509-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Potassium hydrogen tartrate; Kalii bitartaricum; Kalii hydrogentartras

### Special notes

When selecting the *Potassium hydrogen tartrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Potassium hydrogen tartrate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Potassium hydrog... | 11345805 | 20772     | 40      | 20120103    |
| Caelo    | Potassium hydrog... | 15354609 | 23193     | 40      | 20151030    |
| Caelo    | Potassium hydrog... | 170656   | 23285     | 40      | 20170511*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Potassium hydrogen tartrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 310 spectra of 8 reference samples from the substance/substance group *Potassium hydrogen tartrate*.

| Supplier | Substance                   | Batch    | Sample ID | Spectra |
|----------|-----------------------------|----------|-----------|---------|
| Caelo    | Potassium hydrogen tartrate | 11127421 | 20509     | 40      |
| Caelo    | Potassium hydrogen tartrate | 11345805 | 20588     | 40      |
| Caelo    | Potassium hydrogen tartrate | 11345805 | 20611     | 40      |
| Caelo    | Potassium hydrogen tartrate | 11127402 | 20643     | 30      |
| Caelo    | Potassium hydrogen tartrate | 11345805 | 20644     | 40      |
| Caelo    | Potassium hydrogen tartrate | 11345805 | 20645     | 40      |
| Caelo    | Potassium hydrogen tartrate | 17065604 | 23414     | 40      |
| Caelo    | Potassium hydrogen tartrate | 17065603 | 23709     | 40      |

- 146 419 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 22 spectra from 14 *Apo-Ident* customers from 17 batches from the substance/substance group *Potassium hydrogen tartrate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier | Substance                   | Batch     | Spectra |
|----------|-----------------------------|-----------|---------|
| Caelo    | Potassium hydrogen tartrate | 15081008  | 2       |
| Sanacorp | Potassium hydrogen tartrate | 15354609  | 1       |
| Caelo    | Potassium hydrogen tartrate | 13133120  | 2       |
| Caelo    | Potassium hydrogen tartrate | 15081010  | 1       |
| Caelo    | Potassium hydrogen tartrate | 14115208  | 1       |
| Caelo    | Potassium hydrogen tartrate | 160514b   | 1       |
| Caelo    | Potassium hydrogen tartrate | 23062015A | 1       |
| Caelo    | Potassium hydrogen tartrate | 11345805  | 1       |
| Caelo    | Potassium hydrogen tartrate | 11127417  | 1       |
| Caelo    | Potassium hydrogen tartrate | 11345807  | 1       |
| Gehe     | Potassium hydrogen tartrate | 11345808  | 1       |
| Caelo    | Potassium hydrogen tartrate | 13030002  | 1       |
| Caelo    | Potassium hydrogen tartrate | 13030006  | 3       |
| Caelo    | Potassium hydrogen tartrate | 13133104  | 2       |
| Caelo    | Potassium hydrogen tartrate | 13133114  | 1       |
| Caelo    | Potassium hydrogen tartrate | 17061303  | 1       |
| Caelo    | Potassium hydrogen tartrate | 90573259  | 1       |

- 69 611 spectra from 414 *Apo-Ident* customers from a total of 23 784 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Potassium hydrogen tartrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Potassium hydrogen tartrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 310           | 0              | 146 419       |
| <b>Type C</b> | 0              | 21            | 1              | 69 611        |

The substance/substance group *Potassium hydrogen tartrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.0645 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 95.4545 % (> 81.8182 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20772     | 23285               | 3.64                         | 65.16                           |
| 23193     | 23285               | 3.91                         | 65.25                           |
| 23285     | 23285               | 0.00                         | 65.35                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Potassium orotate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20419-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Potassium orotate; Kalii orotas; Kalii oroticum

### Special notes

When selecting the *Potassium orotate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Potassium orotate*:

| Supplier | Substance         | Batch       | Sample ID | Spectra | Certificate |
|----------|-------------------|-------------|-----------|---------|-------------|
| Euro OTC | Potassium orotate | 1203038V-02 | 22335     | 40      | 20150723    |
| Euro OTC | Potassium orotate | 1203038V-02 | 22498     | 40      | 9757        |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Potassium orotate*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1551 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *Potassium orotate*.

| Supplier    | Substance         | Batch       | Sample ID          | Spectra |
|-------------|-------------------|-------------|--------------------|---------|
| Pharmorgana | Potassium orotate | 1000070227  | 20419              | 40      |
| Euro OTC    | Potassium orotate | 1203038V-02 | 22335 <sup>†</sup> | 20      |
| Euro OTC    | Potassium orotate | 1203038V-02 | 22808              | 40      |

- 146 629 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Potassium orotate*.

| Supplier | Substance         | Batch      | Spectra |
|----------|-------------------|------------|---------|
| Euro OTC | Potassium orotate | 1203038-01 | 1       |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Potassium orotate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Potassium orotate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 60            | 40             | 146 629       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Potassium orotate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 60.0000 % (> 57.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22335     | 22498               | 12.48                        | 125.40                          |
| 22498     | 22498               | 0.00                         | 124.52                          |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das

alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Potassium sodium tartrate tetrahydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20782-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Potassium sodium tartrate tetrahydrate; Kalii natrii tartras tetrahydricus; Tartarus natronatus

### Special notes

When selecting the *Potassium sodium tartrate tetrahydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Potassium sodium tartrate tetrahydrate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Potassium sodium... | 12030207 | 20782     | 40      | 20120213    |
| Caelo    | Potassium sodium... | 13216605 | 20998     | 40      | 1404530     |
| Caelo    | Potassium sodium... | 14376001 | 21801     | 40      | 20150204    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Potassium sodium tartrate tetrahydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 72 spectra of 3 reference samples from the substance/substance group *Potassium sodium tartrate tetrahydrate*.

| Supplier | Substance                       | Batch    | Sample ID          | Spectra |
|----------|---------------------------------|----------|--------------------|---------|
| Caelo    | Potassium sodium tartrate te... | 14376001 | 21801 <sup>†</sup> | 20      |
| Caelo    | Potassium sodium tartrate te... | 15375607 | 23207              | 40      |
| Caelo    | Potassium sodium tartrate te... | 15375601 | not required       | 12      |

- 146 657 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Potassium sodium tartrate tetrahydrate*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Potassium sodium tartrate tetrahydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Potassium sodium tartrate tetrahydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 72            | 0              | 146 657       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Potassium sodium tartrate tetrahydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 91.6667 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20782     | 20998               | 4.44                         | 49.42                           |
| 20998     | 20998               | 0.00                         | 49.61                           |
| 21801     | 20998               | 6.71                         | 50.67                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Potassium sorbate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20020-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Potassium sorbate; Kalii sorbas; Kalii sorbinicum

### Special notes

When selecting the *Potassium sorbate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Potassium sorbate*:

| Supplier | Substance         | Batch    | Sample ID | Spectra | Certificate |
|----------|-------------------|----------|-----------|---------|-------------|
| Caelo    | Potassium sorbate | 13224604 | 21444     | 40      | 20130813    |
| Euro OTC | Potassium sorbate | 1508025  | 21892     | 40      | 20150902*   |
| Euro OTC | Potassium sorbate | 1608013  | 22786     | 40      | 20160819*   |
| Caelo    | Potassium sorbate | 163266   | 23059     | 40      | 20170105*   |
| Caelo    | Potassium sorbate | 17170008 | 23585     | 40      | 20170711    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Potassium sorbate*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 235 spectra of 6 reference samples from the substance/substance group *Potassium sorbate*.

| Supplier | Substance         | Batch    | Sample ID          | Spectra |
|----------|-------------------|----------|--------------------|---------|
| Caelo    | Potassium sorbate | 90877159 | 20020              | 75      |
| Caelo    | Potassium sorbate | 11214207 | 20453              | 40      |
| Caelo    | Potassium sorbate | 13224604 | 21444 <sup>†</sup> | 20      |
| Euro OTC | Potassium sorbate | 1508025  | 21892 <sup>†</sup> | 20      |
| Euro OTC | Potassium sorbate | 1703034  | 23176              | 40      |
| Caelo    | Potassium sorbate | 171700   | 23638              | 40      |

- 146 494 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 425 spectra from 221 *Apo-Ident* customers from 100 batches from the substance/substance group *Potassium sorbate*.

| Supplier                   | Substance         | Batch      | Spectra |
|----------------------------|-------------------|------------|---------|
| Caelo                      | Potassium sorbate | 12211107   | 18      |
| Caelo                      | Potassium sorbate | 14380601   | 16      |
| Caelo                      | Potassium sorbate | 14380610   | 16      |
| Caelo                      | Potassium sorbate | 15248204   | 17      |
| Caelo                      | Potassium sorbate | 15248205   | 8       |
| Caelo                      | Potassium sorbate | 14380607   | 7       |
| Caelo                      | Potassium sorbate | 12059909   | 7       |
| Caelo                      | Potassium sorbate | 13065204   | 14      |
| Caelo                      | Potassium sorbate | 13224610   | 1       |
| Caelo                      | Potassium sorbate | 13065217   | 12      |
| Caelo                      | Potassium sorbate | 13224612   | 16      |
| Fiebig                     | Potassium sorbate | 10012210   | 1       |
| Caelo                      | Potassium sorbate | 10012210   | 1       |
| Caelo                      | Potassium sorbate | 10199505   | 1       |
| Caelo                      | Potassium sorbate | 1112331024 | 1       |
| Caelo                      | Potassium sorbate | 13065205   | 17      |
| AHD                        | Potassium sorbate | 13065216   | 1       |
| Caelo                      | Potassium sorbate | 11261304   | 4       |
| Caelo                      | Potassium sorbate | 12211101   | 13      |
| Caelo                      | Potassium sorbate | 9305601    | 2       |
| Caelo                      | Potassium sorbate | 2041402    | 1       |
| Spinnrad GmbH              | Potassium sorbate | 1114331022 | 1       |
| Spinnrad                   | Potassium sorbate | 1114331022 | 3       |
| Fagron                     | Potassium sorbate | 1114331022 | 1       |
| Caelo                      | Potassium sorbate | 11192305   | 1       |
| Caesar/ Noweda             | Potassium sorbate | 12211107   | 2       |
| Caelo                      | Potassium sorbate | 12211108   | 2       |
| Fagron                     | Potassium sorbate | 13065211   | 1       |
| Caelo                      | Potassium sorbate | 13065216   | 13      |
| Caesar & Loretz GmbH Hi... | Potassium sorbate | 13065217   | 2       |
| Caelo                      | Potassium sorbate | 13065222   | 2       |
| Noweda                     | Potassium sorbate | 13065222   | 1       |
| Caelo                      | Potassium sorbate | 13111409   | 1       |
| Euro OTC                   | Potassium sorbate | 1312024-01 | 2       |
| Caelo                      | Potassium sorbate | 1312024-01 | 2       |
| Caelo                      | Potassium sorbate | 13224604   | 15      |
| Sonnenberg-Apotheke        | Potassium sorbate | 13224604   | 1       |
| Ichthyol/Noweda            | Potassium sorbate | 13224604   | 1       |
| Caelo                      | Potassium sorbate | 13224608   | 2       |
| Caelo                      | Potassium sorbate | 13224611   | 9       |
| Apomix/Noweda              | Potassium sorbate | 13224611   | 1       |
| Sanacorp                   | Potassium sorbate | 13224611   | 1       |
| Anzag 12.01.15             | Potassium sorbate | 13224611   | 1       |
| Euro OTC                   | Potassium sorbate | 13224612   | 1       |
| sana                       | Potassium sorbate | 13224612   | 1       |
| Caelo                      | Potassium sorbate | 13277804   | 1       |
| Euro OTC                   | Potassium sorbate | 1410020-01 | 1       |
| Caelo                      | Potassium sorbate | 1438060    | 1       |
| Caelo                      | Potassium sorbate | 14380602   | 2       |
| Caelo                      | Potassium sorbate | 14380606   | 7       |
| Caelo                      | Potassium sorbate |            | 1       |
| Caesar&Loretz GmbH/Sana... | Potassium sorbate | 14380607   | 1       |
| Phoenix                    | Potassium sorbate | 14380610   | 1       |
| Caelo                      | Potassium sorbate | 14380612   | 1       |
| Caelo                      | Potassium sorbate | 14380620   | 1       |
| Caelo                      | Potassium sorbate | 14380621   | 8       |

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| <b>Supplier</b>            | <b>Substance</b>  | <b>Batch</b> | <b>Spectra</b> |
|----------------------------|-------------------|--------------|----------------|
| Caesar & Loretz/Noweda     | Potassium sorbate | 14380621     | 1              |
| Caelo                      | Potassium sorbate | 14380622     | 7              |
| Fagron                     | Potassium sorbate | 14380622     | 1              |
| Caelo                      | Potassium sorbate | 14380627     | 7              |
| Caesar&Loretz GmbH         | Potassium sorbate | 14380622     | 1              |
| Caesar & Loretz GmbH       | Potassium sorbate | 14380627     | 1              |
| Caelo                      | Potassium sorbate | 14380632     | 4              |
| Phoenix                    | Potassium sorbate | 14380627     | 1              |
| Caelo                      | Potassium sorbate | 14380633     | 5              |
| Caelo                      | Potassium sorbate | 14380635     | 5              |
| Caelo                      | Potassium sorbate | 1438610      | 1              |
| Euro OTC                   | Potassium sorbate | 1508025-01   | 7              |
| Caelo                      | Potassium sorbate | 15248203     | 1              |
| Caelo                      | Potassium sorbate | 15382105     | 7              |
| Caesar & Loretz GmbH Hi... | Potassium sorbate | 15382105     | 1              |
| Caelo                      | Potassium sorbate | 15382114     | 5              |
| Caelo                      | Potassium sorbate | 15382115     | 3              |
| Caelo                      | Potassium sorbate | 16326602     | 1              |
| Caelo                      | Potassium sorbate | 16326606     | 2              |
| Gehe                       | Potassium sorbate | 16326606     | 1              |
| Caelo                      | Potassium sorbate | 16326607     | 3              |
| Caelo                      | Potassium sorbate | 16326608     | 2              |
| Caelo                      | Potassium sorbate | 16326609     | 1              |
| Caelo                      | Potassium sorbate | 17170007     | 1              |
| Spinnrad GmbH              | Potassium sorbate | 214331021    | 1              |
| Euro OTC                   | Potassium sorbate | 216331021    | 1              |
| spinnrad/gehe              | Potassium sorbate | 216331021    | 1              |
| Fagron                     | Potassium sorbate | 3115M-01748  | 1              |
| Spinnrad/Gehe              | Potassium sorbate | 315331021    | 1              |
| Spinnrad/Sanacorp          | Potassium sorbate | 315331021    | 2              |
| Spinnrad                   | Potassium sorbate | 315331021    | 2              |
| Fagron                     | Potassium sorbate | 3912A-01748  | 1              |
| Spinnrad/Sannacorp         | Potassium sorbate | 616331022    | 1              |
| Spinnrad                   | Potassium sorbate | 616331022    | 1              |
| Fagron                     | Potassium sorbate | 4314U-01748  | 1              |
| Spinnrad                   | Potassium sorbate | 815331022    | 1              |
| Spinnrad                   | Potassium sorbate | 912331023    | 2              |
| Fagron                     | Potassium sorbate | 912331023    | 2              |
| Caelo                      | Potassium sorbate | AKD12        | 1              |
| Phönix Gotha               | Potassium sorbate |              | 1              |
| Spinnrad GmbH              | Potassium sorbate | 111033102    | 1              |
| Euro OTC                   | Potassium sorbate | 111103802    | 1              |
|                            | Potassium sorbate | 10012203     | 1              |
| Spinnrad                   | Potassium sorbate | 111033102    | 1              |
| Euro OTC                   | Potassium sorbate | 1111038-01   | 1              |
| Euro OTC                   | Potassium sorbate | 1111038-02   | 2              |
| spinnrad gmbh              | Potassium sorbate | 1111331023   | 1              |
| Caelo                      | Potassium sorbate | 11214207     | 1              |
| Caesar & Loretz GmbH       | Potassium sorbate | 11261303     | 1              |
| Gehe                       | Potassium sorbate | 11261304     | 1              |
| Caelo                      | Potassium sorbate | 12059902     | 1              |
| Caelo                      | Potassium sorbate | 12059905     | 4              |
| Caelo                      | Potassium sorbate | 12059908     | 1              |
| Phoenix, 11.09.2012        | Potassium sorbate | 12059909     | 1              |
| Caelo                      | Potassium sorbate | 12059914     | 3              |
| Caelo                      | Potassium sorbate | 1205999      | 1              |
| Caelo                      | Potassium sorbate | 1221101      | 1              |
| Caelo                      | Potassium sorbate | 1221107      | 1              |
| Noweda                     | Potassium sorbate | 12211101     | 1              |
| Sanacorp                   | Potassium sorbate | 12211101     | 1              |

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| Supplier               | Substance         | Batch       | Spectra |
|------------------------|-------------------|-------------|---------|
| Caelo                  | Potassium sorbate | 12211102    | 5       |
| Noweda                 | Potassium sorbate | 12211107    | 1       |
| Kehr                   | Potassium sorbate | 12211107    | 1       |
| Holderman 24.01.2013   | Potassium sorbate | 12211107    | 2       |
| Caelo                  | Potassium sorbate | 12211121    | 4       |
| Caelo                  | Potassium sorbate | 12211123    | 1       |
| Caelo                  | Potassium sorbate | 12345       | 1       |
| Gehe 08.05.2013        | Potassium sorbate | 13065204    | 1       |
| Caesar/Lorenz          | Potassium sorbate | 13065204    | 1       |
| phonix                 | Potassium sorbate | 13065205    | 1       |
| Gehe                   | Potassium sorbate | 13065205    | 1       |
| Caelo                  | Potassium sorbate | 13065211    | 1       |
| canea, gehe            | Potassium sorbate | 13065215    | 1       |
| Gehe                   | Potassium sorbate | 13065216    | 2       |
| Sanacorp               | Potassium sorbate | 13065217    | 1       |
| Phoenix                | Potassium sorbate | 1397235     | 1       |
| Spinnrad               | Potassium sorbate | 1901211748  | 1       |
| Caelo                  | Potassium sorbate | 20021112-2  | 1       |
| RFI Food Ingredients   | Potassium sorbate | 2006383927  | 1       |
| Caelo                  | Potassium sorbate | 200613K1    | 1       |
| Caelo                  | Potassium sorbate | 2912M-01748 | 2       |
| Spinnrad               | Potassium sorbate | 312331021   | 3       |
| Caelo                  | Potassium sorbate | 3512M-01748 | 1       |
| siehe WE-Prüfprotokoll | Potassium sorbate | 61/11       | 1       |
| Spinnrad GmbH          | Potassium sorbate | 912331023   | 2       |
| Caelo                  | Potassium sorbate | 912331023   | 1       |
| Caelo                  | Potassium sorbate | 91623299    | 2       |
| Caelo                  | Potassium sorbate | K-010213-1  | 1       |
| Caelo                  | Potassium sorbate | AKD10       | 1       |
| s.Prüfprotokoll        | Potassium sorbate |             | 1       |

- 69 208 spectra from 414 *Apo-Ident* customers from a total of 23 707 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Potassium sorbate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Potassium sorbate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 231           | 4              | 146 494       |
| <b>Type C</b> | 0              | 407           | 18             | 69 208        |

The substance/substance group *Potassium sorbate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 98.2979 % (> 97.0213 %)  |
| Type C | 100.0000 % (> 99.8812 %) | 95.7647 % (> 95.0588 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21444     | 21892               | 14.89                        | 38.12                           |
| 21892     | 21892               | 0.00                         | 38.40                           |
| 22786     | 22786               | 0.00                         | 40.10                           |
| 23059     | 23059               | 0.00                         | 34.83                           |
| 23585     | 23059               | 9.78                         | 35.88                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Potassium tartrate hemihydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20999-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Potassium tartrate hemihydrate; Kalii tartaricum; Kalii tartras hemihydricus

### Special notes

When selecting the *Potassium tartrate hemihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Potassium tartrate hemihydrate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Potassium tartra... | 13331101 | 20999     | 40      | 1403536     |
| Caelo    | Potassium tartra... | 13331104 | 21440     | 40      | 20131002    |
| Caelo    | Potassium tartra... | 15167701 | 21812     | 40      | 20150608    |
| Caelo    | Potassium tartra... | 160289   | 22462     | 40      | 20160405*   |



## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Potassium tartrate hemihydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 4 reference samples from the substance/substance group *Potassium tartrate hemihydrate*.

| Supplier | Substance                      | Batch    | Sample ID          | Spectra |
|----------|--------------------------------|----------|--------------------|---------|
| Caelo    | Potassium tartrate hemihydrate | 11225007 | 20623              | 40      |
| Caelo    | Potassium tartrate hemihydrate | 13331104 | 21440 <sup>†</sup> | 20      |
| Caelo    | Potassium tartrate hemihydrate | 15167701 | 21812 <sup>†</sup> | 20      |
| Caelo    | Potassium tartrate hemihydrate | 160289   | 22462 <sup>†</sup> | 20      |

- 146 629 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 8 spectra from 3 *Apo-Ident* customers from 8 batches from the substance/substance group *Potassium tartrate hemihydrate*.

| Supplier | Substance                      | Batch    | Spectra |
|----------|--------------------------------|----------|---------|
| Caelo    | Potassium tartrate hemihydrate | 12322105 | 1       |
| Caelo    | Potassium tartrate hemihydrate | 15167703 | 1       |
| Caelo    | Potassium tartrate hemihydrate | 11225007 | 1       |
| Caelo    | Potassium tartrate hemihydrate | 13331113 | 1       |
| Caelo    | Potassium tartrate hemihydrate | 13111415 | 1       |
| Caelo    | Potassium tartrate hemihydrate | 13331109 | 1       |
| Caelo    | Potassium tartrate hemihydrate | 12322110 | 1       |
| Caelo    | Potassium tartrate hemihydrate | 27061304 | 1       |

- 69 625 spectra from 414 *Apo-Ident* customers from a total of 23 793 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Potassium tartrate hemihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Potassium tartrate hemihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 100           | 0              | 146 629       |
| <b>Type C</b> | 0              | 8             | 0              | 69 625        |

The substance/substance group *Potassium tartrate hemihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested

reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20999     | 20999               | 0.00                         | 42.53                           |
| 21440     | 20999               | 3.42                         | 40.25                           |
| 21812     | 22462               | 4.97                         | 40.21                           |
| 22462     | 22462               | 0.00                         | 42.37                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Povidone 25, soluble**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20684-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Povidone 25, soluble; Povidonum 25, solubile

### Special notes

When selecting the *Povidone 25, soluble* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Povidone 25, soluble*:

| Supplier | Substance             | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------------------|------------------|-----------|---------|--------------------|
| Caelo    | Povidone 25, sol. ... | 12032714         | 20684     | 40      | 1402437            |
| Fagron   | Povidone 25, sol. ... | 12E22-N05        | 20770     | 40      | 1411537            |
| Caelo    | Povidone 25, sol. ... | 14142103         | 21378     | 40      | AR-15-FG-000596-01 |
| Fagron   | Povidone 25, sol. ... | 13J21-N02        | 22731     | 40      | AR-16-FG-019116-01 |
| Caelo    | Povidone 25, sol. ... | 16307808         | 23255     | 40      | AR-17-FG-015299-02 |
| Fagron   | Povidone 25, sol. ... | 15C12-B02-323006 | 23265     | 40      | 1710348            |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Povidone 25, soluble*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 110 spectra of 3 reference samples from the substance/substance group *Povidone 25, soluble*.

| Supplier | Substance            | Batch     | Sample ID | Spectra |
|----------|----------------------|-----------|-----------|---------|
| Fagron   | Povidone 25, soluble | 12B07-N04 | 20559     | 40      |
| Fagron   | Povidone 25, soluble | 12B07-N04 | 20635     | 40      |
| Caelo    | Povidone 25, soluble | 172091    | 23619     | 30      |

- 146 619 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 22 spectra from 9 *Apo-Ident* customers from 12 batches from the substance/substance group *Povidone 25, soluble*.

| Supplier | Substance            | Batch    | Spectra |
|----------|----------------------|----------|---------|
| Caelo    | Povidone 25, soluble | 14142103 | 1       |
| Caelo    | Povidone 25, soluble | 14142109 | 3       |
| Caelo    | Povidone 25, soluble | 12032714 | 1       |

*continued on the next page*

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| Supplier | Substance            | Batch     | Spectra |
|----------|----------------------|-----------|---------|
| Caelo    | Povidone 25, soluble | 14207508  | 3       |
| Caelo    | Povidone 25, soluble | 14207511  | 4       |
| Caelo    | Povidone 25, soluble | 14207515  | 1       |
| Caelo    | Povidone 25, soluble | 15383101  | 3       |
| Caelo    | Povidone 25, soluble | 16051101  | 1       |
| Fagron   | Povidone 25, soluble | 15C12-B02 | 1       |
| Caelo    | Povidone 25, soluble | 12376301  | 1       |
| Caelo    | Povidone 25, soluble | 15383102  | 1       |
| Caelo    | Povidone 25, soluble | 13323407  | 2       |

- 69 611 spectra from 414 *Apo-Ident* customers from a total of 23 789 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Povidone 25, soluble* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Povidone 25, soluble* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 29            | 81             | 146 619       |
| <b>Type C</b> | 0              | 20            | 2              | 69 611        |

The substance/substance group *Povidone 25, soluble* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 26.3636 % (> 23.6364 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 90.9091 % (> 77.2727 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20684     | 20684               | 0.00                         | 18.50                           |
| 20770     | 20770               | 0.00                         | 22.46                           |
| 21378     | 21378               | 0.00                         | 17.34                           |
| 22731     | 22731               | 0.00                         | 23.01                           |
| 23255     | 23255               | 0.00                         | 14.14                           |
| 23265     | 23265               | 0.00                         | 14.60                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Povidone iodine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20472-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Povidone iodine; Polyvinylpyrrolidoni jodum; Povidonum iodinum

### Special notes

When selecting the *Povidone iodine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Povidone iodine*:

| Supplier | Substance       | Batch      | Sample ID | Spectra | Certificate        |
|----------|-----------------|------------|-----------|---------|--------------------|
| Caelo    | Povidone iodine | 13337205   | 21466     | 40      | 20131021           |
| Euro OTC | Povidone iodine | 1501029-01 | 21777     | 40      | 20150211           |
| Euro OTC | Povidone iodine | 1509009    | 21908     | 40      | 20150918*          |
| Caelo    | Povidone iodine | 15234101   | 23252     | 40      | AR-17-FG-015433-02 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Povidone iodine*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 300 spectra of 9 reference samples from the substance/substance group *Povidone iodine*.

| Supplier | Substance       | Batch      | Sample ID          | Spectra |
|----------|-----------------|------------|--------------------|---------|
| Caelo    | Povidone iodine | 10090613   | 20202              | 40      |
| Caelo    | Povidone iodine | 10090618   | 20472              | 40      |
| Euro OTC | Povidone iodine | 1110013-02 | 21073              | 40      |
| Caelo    | Povidone iodine | 13337205   | 21466 <sup>†</sup> | 20      |
| Euro OTC | Povidone iodine | 1501029-01 | 21777 <sup>†</sup> | 20      |
| Euro OTC | Povidone iodine | 1509009    | 21908 <sup>†</sup> | 20      |
| Euro OTC | Povidone iodine | 1606026    | 22675              | 40      |
| Caelo    | Povidone iodine | 15234109   | 23256              | 40      |
| Euro OTC | Povidone iodine | 1704007    | 23435              | 40      |

- 146 429 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 54 spectra from 23 *Apo-Ident* customers from 29 batches from the substance/substance group *Povidone iodine*.

| Supplier      | Substance       | Batch      | Spectra |
|---------------|-----------------|------------|---------|
| Herbasinica   | Povidone iodine | 10090619   | 1       |
| Phönix        | Povidone iodine | 1110013-02 | 1       |
| Euro OTC      | Povidone iodine | 1509009-02 | 1       |
| Caelo         | Povidone iodine | 11168607   | 1       |
| Stumpf        | Povidone iodine | 11168612   | 1       |
| Caelo         | Povidone iodine | 12153110   | 2       |
| Caelo         | Povidone iodine | 12153106   | 2       |
| Caelo         | Povidone iodine | 11168612   | 1       |
| Caelo         | Povidone iodine | 12072605   | 1       |
| Caelo         | Povidone iodine | 12153116   | 2       |
| Caelo         | Povidone iodine | 12153119   | 2       |
| Fagron        | Povidone iodine | 1110013-02 | 1       |
| Euro OTC      | Povidone iodine | 130901001  | 1       |
| Euro OTC      | Povidone iodine | 1407032-01 | 5       |
| Euro OTC      | Povidone iodine | 1401029-01 | 1       |
| Caelo         | Povidone iodine | 14195810   | 3       |
| Caelo         | Povidone iodine | 14195813   | 2       |
| BASF/Phönix   | Povidone iodine | 1501029-01 | 3       |
| Euro OTC      | Povidone iodine | 1501029-01 | 1       |
| Euro OTC      | Povidone iodine | 1509009-01 | 1       |
| Caelo         | Povidone iodine | 15121402   | 1       |
| Caelo         | Povidone iodine | 15234101   | 1       |
| Caelo         | Povidone iodine | 15234109   | 1       |
| Euro OTC      | Povidone iodine | 1603023-01 | 1       |
| Euroo/Phoenix | Povidone iodine | G3115BPZ0  | 1       |
| Euro OTC      | Povidone iodine | 1704007-01 | 2       |
| Euro OTC      | Povidone iodine | G4208BPZ0  | 2       |
| Euro OTC      | Povidone iodine | 110013-02  | 1       |
| Euro OTC      | Povidone iodine | 1110013-02 | 4       |
| Euro OTC      | Povidone iodine | 111001302  | 1       |
| BASF, Noweda  | Povidone iodine | 1110013-02 | 2       |
| Caelo         | Povidone iodine | 19061302   | 1       |
| Noweda        | Povidone iodine | G0354BPZ0  | 1       |
| Euro OTC      | Povidone iodine | 1005049-02 | 1       |
| Caelo         | Povidone iodine | 1110013-02 | 1       |

- 69 579 spectra from 414 *Apo-Ident* customers from a total of 23 773 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Povidone iodine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Povidone iodine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following

table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 280           | 20             | 146 429       |
| <b>Type C</b> | 0              | 48            | 6              | 69 579        |

The substance/substance group *Povidone iodine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 93.3333 % (> 92.3333 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 88.8889 % (> 83.3333 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21466     | 21908               | 6.06                         | 24.39                           |
| 21777     | 21908               | 5.61                         | 21.28                           |
| 21908     | 21908               | 0.00                         | 22.20                           |
| 23252     | 23252               | 0.00                         | 21.22                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Prasterone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20703-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Prasterone; Prasteronum

### Special notes

When selecting the *Prasterone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Prasterone*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate |
|----------|------------|------------------|-----------|---------|-------------|
| Euro OTC | Prasterone | 1102036-01       | 20703     | 40      | 1404310     |
| Fagron   | Prasterone | 13J10-B02-287175 | 20960     | 40      | 1404309     |
| Euro OTC | Prasterone | 1506011          | 21824     | 40      | 20150629*   |
| Fagron   | Prasterone | 15G14-B07-310827 | 21917     | 40      | 20150814    |
| Euro OTC | Prasterone | 1602018          | 22506     | 30      | 20160301*   |
| Euro OTC | Prasterone | 1704012          | 23389     | 40      | 20170529*   |
| Euro OTC | Prasterone | 1707014          | 23695     | 40      | 20170829*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 270 spectra of 7 reference samples from the substance/substance group *Prasterone*. These samples are listed above in the [calibration samples](#) section.
- 71 116 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 360 spectra of 9 reference samples from the substance/substance group *Prasterone*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Fagron   | Prasterone | 10L22-N12        | 20445              | 40      |
| Fagron   | Prasterone | 10L22-N12        | 20527              | 40      |
| Euro OTC | Prasterone | 1506011          | 21824 <sup>†</sup> | 20      |
| Fagron   | Prasterone | 15G14-B07-310827 | 21917 <sup>†</sup> | 20      |
| Euro OTC | Prasterone | 1702025          | 23147              | 40      |
| Euro OTC | Prasterone | 1506011          | 21824SI            | 60      |
| Fagron   | Prasterone | 15G14-B07-310827 | 21917SI            | 60      |
| Euro OTC | Prasterone | 1602018          | 22506SI            | 40      |
| Euro OTC | Prasterone | 1702025          | 23147SI            | 40      |

- 146 369 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 71 spectra from 25 *Apo-Ident* customers from 44 batches from the substance/substance group *Prasterone*.

| Supplier                   | Substance  | Batch             | Spectra |
|----------------------------|------------|-------------------|---------|
| Fagron                     | Prasterone | 14H12-B05-297727  | 2       |
| Fagron                     | Prasterone | 15G14-B07-310827  | 1       |
| Audor Pharma               | Prasterone | 10050051/1P       | 1       |
| Euro OTC                   | Prasterone | 1102036-01        | 1       |
| Euro OTC                   | Prasterone | 1409004-01        | 4       |
| Euro OTC                   | Prasterone | 1412028-01        | 2       |
| Audor Pharma               | Prasterone | AP11040002P       | 3       |
| Euro OTC                   | Prasterone | 2081302           | 1       |
| Euro OTC                   | Prasterone | 4091511           | 1       |
| Nachprüfung                | Prasterone | 120022            | 1       |
| Fagron                     | Prasterone | 12C26-N09         | 1       |
| Euro OTC                   | Prasterone | 1203010-01        | 2       |
| Fagron                     | Prasterone | 12K30-N06         | 3       |
| Fagron                     | Prasterone | 12G04-N19         | 2       |
| Fragon                     | Prasterone | 12G04-N19         | 1       |
| Euro OTC                   | Prasterone | 1306021-01        | 4       |
| Euro OTC                   | Prasterone | 1311002-01        | 3       |
| EuRho                      | Prasterone | 1311002-01        | 1       |
| Fagron                     | Prasterone | 13J10-B02         | 1       |
| Euro OTC                   | Prasterone | 1401040-01        | 3       |
| Euro OTC                   | Prasterone | 140900401         | 1       |
| Euro OTC                   | Prasterone | 1412028           | 1       |
| Fagron                     | Prasterone | 14C18-B02         | 1       |
| Caelo                      | Prasterone | 1412028-01        | 1       |
| Fagron                     | Prasterone | 14C18-Bo2-293603  | 1       |
| Fagron                     | Prasterone | 14C18-B02-293606  | 1       |
| Fagron                     | Prasterone | 14J21-B03-303458  | 1       |
| Euro OTC                   | Prasterone | 1506011-01        | 2       |
| Fagron                     | Prasterone | 16B19-B04         | 1       |
| Euro OTC                   | Prasterone | 1602018-02        | 1       |
| Fagron                     | Prasterone | 19061304          | 1       |
| Caelo                      | Prasterone | 16B19-B04-318665  | 1       |
| Fagron                     | Prasterone | 16B19-B04-318665  | 1       |
| Caelo                      | Prasterone | 16I02-B02-326485  | 1       |
| Caelo                      | Prasterone | 16I02-B02-326485  | 2       |
| Haihang                    | Prasterone | 20130507          | 1       |
| Haihang Industry           | Prasterone | 20130816          | 4       |
| Euro OTC                   | Prasterone | 22021306          | 1       |
| Euro OTC                   | Prasterone | 30041509          | 1       |
| Euro OTC                   | Prasterone | 26031506          | 1       |
| Fagron                     | Prasterone | 7013260004        | 1       |
| Fagron                     | Prasterone | L14050137         | 1       |
| Euro OTC                   | Prasterone | 9215-4/09         | 1       |
| NWM Shandong Northwest ... | Prasterone | PST151207         | 1       |
| Caelo                      | Prasterone | T03-04            | 1       |
| Euro OTC                   | Prasterone | XPC0263           | 1       |
| Fagron                     | Prasterone | 13J10-B02-287177  | 1       |
| Euro OTC                   | Prasterone | T03-04/1412028-01 | 1       |

- 69 562 spectra from 414 *Apo-Ident* customers from a total of 23 757 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Prasterone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Prasterone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 270           | 0              | 71 116        |
| <b>Type B</b> | 0              | 303           | 57             | 146 369       |
| <b>Type C</b> | 0              | 70            | 1              | 69 562        |

The substance/substance group *Prasterone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.7778 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 84.1667 % (> 83.3333 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 98.5915 % (> 94.3662 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20703     | 20703               | 0.00                         | 54.74                           |
| 20960     | 20960               | 0.00                         | 54.97                           |
| 21824     | 21824               | 0.00                         | 55.21                           |
| 21917     | 21824               | 15.67                        | 53.59                           |
| 22506     | 22506               | 0.00                         | 55.39                           |
| 23389     | 23389               | 0.00                         | 23.51                           |
| 23695     | 23695               | 0.00                         | 43.91                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe

mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Prednicarbate, micronized**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20196-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Prednicarbate, micronized; Prednicarbatum micronisatum

### Special notes

When selecting the *Prednicarbate, micronized* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Prednicarbate, micronized*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate        |
|----------|---------------------|-----------|-----------|---------|--------------------|
| Fagron   | Prednicarbate, m... | 12D27-N04 | 20700     | 40      | 20120509           |
| Caelo    | Prednicarbate, m... | 13119402  | 20832     | 35      | 1501576            |
| Caelo    | Prednicarbate, m... | 13119402  | 20833     | 40      | 20130517           |
| Caelo    | Prednicarbate, m... | 13372404  | 21368     | 40      | AR-15-FG-007941-02 |
| Caelo    | Prednicarbate, m... | 13372404  | 21369     | 40      | 20131119           |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Prednicarbate, m... | 14A27-B02-291256 | 21572     | 40      | AR-16-FG-011442-01 |
| Euro OTC | Prednicarbate, m... | 1302033-02       | 21610     | 40      | 1509286            |
| Euro OTC | Prednicarbate, m... | 1507011          | 21858     | 35      | 20150730*          |
| Euro OTC | Prednicarbate, m... | 1601058          | 22366     | 30      | 20160223*          |
| Fagron   | Prednicarbate, m... | 12D27-N04        | 20700SI   | 33      | 20120509           |
| Caelo    | Prednicarbate, m... | 13119402         | 20833SI   | 20      | 20130517           |
| Caelo    | Prednicarbate, m... | 13372404         | 21369SI   | 23      | 20131119           |
| Euro OTC | Prednicarbate, m... | 1601058          | 22366SI   | 21      | 20160223*          |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 437 spectra of 13 reference samples from the substance/substance group *Prednicarbate, micronized*. These samples are listed above in the [calibration samples](#) section.
- 70949 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 609 spectra of 23 reference samples from the substance/substance group *Prednicarbate, micronized*.

| Supplier | Substance                 | Batch            | Sample ID          | Spectra |
|----------|---------------------------|------------------|--------------------|---------|
| Fagron   | Prednicarbate, micronized | 10J04-N10        | 20196              | 40      |
| Fagron   | Prednicarbate, micronized | 14A27-B02-291256 | 21572 <sup>†</sup> | 20      |
| Euro OTC | Prednicarbate, micronized | 1302033-02       | 21610 <sup>†</sup> | 20      |
| Euro OTC | Prednicarbate, micronized | 1507011          | 21858 <sup>†</sup> | 19      |
| Euro OTC | Prednicarbate, micronized | 1601058          | 22366 <sup>†</sup> | 15      |
| Caelo    | Prednicarbate, micronized | 160874           | 22447              | 60      |
| Euro OTC | Prednicarbate, micronized | 1605001          | 22558              | 30      |
| Euro OTC | Prednicarbate, micronized | 1607012          | 22703              | 40      |
| Euro OTC | Prednicarbate, micronized | 1609022          | 22860              | 40      |
| Caelo    | Prednicarbate, micronized | 170138           | 23040              | 40      |
| Euro OTC | Prednicarbate, micronized | 1707022          | 23540              | 40      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

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| Supplier | Substance                 | Batch            | Sample ID            | Spectra |
|----------|---------------------------|------------------|----------------------|---------|
| Fagron   | Prednicarbate, micronized | 12D27-N04        | 20700SI <sup>†</sup> | 15      |
| Caelo    | Prednicarbate, micronized | 13119402         | 20833SI <sup>†</sup> | 10      |
| Caelo    | Prednicarbate, micronized | 13372404         | 21369SI <sup>†</sup> | 10      |
| Fagron   | Prednicarbate, micronized | 14A27-B02-291256 | 21572SI              | 36      |
| Euro OTC | Prednicarbate, micronized | 1507011          | 21858SI              | 15      |
| Euro OTC | Prednicarbate, micronized | 1601058          | 22366SI <sup>†</sup> | 10      |
| Caelo    | Prednicarbate, micronized | 160874           | 22447SI              | 30      |
| Euro OTC | Prednicarbate, micronized | 1605001          | 22558SI              | 25      |
| Euro OTC | Prednicarbate, micronized | 1607012          | 22703SI              | 28      |
| Euro OTC | Prednicarbate, micronized | 1609022          | 22860SI              | 27      |
| Caelo    | Prednicarbate, micronized | 170138           | 23040SI              | 20      |
| Euro OTC | Prednicarbate, micronized | 1707022          | 23540SI              | 19      |

- 146 120 spectra from a total of 3180 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 353 spectra from 141 *Apo-Ident* customers from 130 batches from the substance/substance group *Prednicarbate, micronized*.

| Supplier      | Substance                 | Batch     | Spectra |
|---------------|---------------------------|-----------|---------|
| Fagron        | Prednicarbate, micronized | 10J04-N10 | 1       |
| Fagron        | Prednicarbate, micronized | 8081403   | 1       |
| Fagron        | Prednicarbate, micronized | 11D29-N06 | 1       |
| Fagron        | Prednicarbate, micronized | 11L23-N07 | 6       |
| Caelo         | Prednicarbate, micronized | 9764897   | 1       |
| Caelo         | Prednicarbate, micronized | 12383305  | 1       |
| Caelo         | Prednicarbate, micronized | 13/23-N04 | 1       |
| Caelo         | Prednicarbate, micronized | 13119402  | 2       |
| Fagron        | Prednicarbate, micronized | 13/23-N04 | 3       |
| Caelo         | Prednicarbate, micronized | 13119401  | 1       |
| Caelo         | Prednicarbate, micronized | 13224401  | 6       |
| Sino Phyto    | Prednicarbate, micronized | 13224401  | 1       |
| Caelo         | Prednicarbate, micronized | 13224406  | 1       |
| Caelo         | Prednicarbate, micronized | 13372403  | 9       |
| Caelo         | Prednicarbate, micronized | 13372408  | 1       |
| Fagron        | Prednicarbate, micronized | 13372408  | 1       |
| Caelo         | Prednicarbate, micronized | 13372410  | 4       |
| Apomix/Noweda | Prednicarbate, micronized | 13372410  | 2       |
| Caelo         | Prednicarbate, micronized | 13372419  | 4       |
| Caelo         | Prednicarbate, micronized | 13372411  | 2       |
| Fagron        | Prednicarbate, micronized | 13I23-N04 | 6       |
| Fagron        | Prednicarbate, micronized | 13g05-n03 | 1       |
| Fagron        | Prednicarbate, micronized | 14A27-B02 | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier             | Substance                 | Batch            | Spectra |
|----------------------|---------------------------|------------------|---------|
| Fagron               | Prednicarbate, micronized | 14A27-B02-291256 | 17      |
| Fagron               | Prednicarbate, micronized | 14a27-b02-291256 | 2       |
| Fagron               | Prednicarbate, micronized | 14A27B02291256   | 1       |
| Fagron               | Prednicarbate, micronized | 14A27-B02-291258 | 2       |
| Fagron               | Prednicarbate, micronized | 14A27-B02-295796 | 8       |
| Fagron               | Prednicarbate, micronized | 14A27-B02-295793 | 1       |
| Caelo                | Prednicarbate, micronized | 14A27-B02-295796 | 1       |
| Fagron               | Prednicarbate, micronized | 14A27-B02-295797 | 4       |
| Fagron               | Prednicarbate, micronized | 14J16B06         | 1       |
| Fagron               | Prednicarbate, micronized | 14B13-B31-291255 | 1       |
| Fagron               | Prednicarbate, micronized | 14J16-B06-303465 | 13      |
| Fagron               | Prednicarbate, micronized | 14J16-B06303465  | 1       |
| Fagron               | Prednicarbate, micronized | 14J16B06303466   | 1       |
| Fagron               | Prednicarbate, micronized | 14J16-Bo6303465  | 1       |
| Euro OTC             | Prednicarbate, micronized | 1501033-02       | 2       |
| Caelo                | Prednicarbate, micronized | 1507011-01       | 1       |
| Euro OTC             | Prednicarbate, micronized | 1507011-01       | 1       |
| Euro OTC             | Prednicarbate, micronized | 1507011-02       | 2       |
| Caelo                | Prednicarbate, micronized | 15181403         | 14      |
| Caelo                | Prednicarbate, micronized | 1517E-03595      | 1       |
| Hedinger/ Sanacorp   | Prednicarbate, micronized | 15181403         | 1       |
| Caelo                | Prednicarbate, micronized | 15181404         | 3       |
| Apotärze             | Prednicarbate, micronized | 15181409         | 1       |
| Caelo                | Prednicarbate, micronized | 15181409         | 4       |
| Caelo                | Prednicarbate, micronized | 15181411         | 3       |
| Caelo                | Prednicarbate, micronized | 15446301         | 17      |
| caesar&loretz,Phönix | Prednicarbate, micronized | 15181411         | 1       |
| Noweda               | Prednicarbate, micronized | 15446301         | 1       |
| Caelo                | Prednicarbate, micronized | 15446302         | 9       |
| Caelo                | Prednicarbate, micronized | 15446303         | 3       |
| Caelo                | Prednicarbate, micronized | 15446305         | 2       |
| Caelo                | Prednicarbate, micronized | 15446306         | 7       |
| E und J, 22.07.2016  | Prednicarbate, micronized | 15446306         | 2       |
| Caelo                | Prednicarbate, micronized | 15D15-B03        | 1       |
| Fagron               | Prednicarbate, micronized | 15D15-B03-308161 | 4       |
| Caelo                | Prednicarbate, micronized | 15D15-B03-308161 | 2       |
| Fagron               | Prednicarbate, micronized | 15G10-B02        | 1       |
| Fagron               | Prednicarbate, micronized | 15G10-B02-310848 | 2       |
| Fagron               | Prednicarbate, micronized | 15D15-B03-309682 | 1       |
| Fagron               | Prednicarbate, micronized | 15G10-B02-31084  | 1       |
| Fagron               | Prednicarbate, micronized | 15G10-B02-311819 | 1       |
| Fagron               | Prednicarbate, micronized | 15G10-B02-314082 | 4       |
| Fagron               | Prednicarbate, micronized | 15J22-B04-316799 | 3       |
| Fagron               | Prednicarbate, micronized | 15J22-B04        | 1       |
| Fagron               | Prednicarbate, micronized | 15J22-B04-318528 | 3       |
| Fagron               | Prednicarbate, micronized | 15J22-B04-318930 | 1       |
| Phönix               | Prednicarbate, micronized | 15J22-B04-318528 | 1       |
| Fargon               | Prednicarbate, micronized | 15J22-B04-318930 | 1       |
| Fagron               | Prednicarbate, micronized | 15J22-B04-321005 | 1       |
| Fagron               | Prednicarbate, micronized | 15J-B04-316799   | 1       |
| Fagron               | Prednicarbate, micronized | 16/27-B01-332958 | 1       |
| Euro OTC             | Prednicarbate, micronized | 1601058-01       | 4       |
| Euro OTC             | Prednicarbate, micronized | 1605001-01       | 5       |
| Euro OTC             | Prednicarbate, micronized | 1605001          | 1       |
| Sonnenberg-Apotheke  | Prednicarbate, micronized | 1607012-01       | 1       |
| Euro OTC             | Prednicarbate, micronized | 1607012-01       | 2       |
| Caelo                | Prednicarbate, micronized | 16087401         | 4       |
| Caelo                | Prednicarbate, micronized | 1608710          | 1       |
| Caelo                | Prednicarbate, micronized | 16087408         | 4       |
| Caelo                | Prednicarbate, micronized | 16087410         | 3       |

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| <b>Supplier</b>            | <b>Substance</b>          | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|---------------------------|------------------|----------------|
| caesar&lorenz GmbH,AHC,... | Prednicarbate, micronized | 16087408         | 1              |
| Caelo                      | Prednicarbate, micronized | 16087412         | 2              |
| Caelo                      | Prednicarbate, micronized | 1609022-01       | 3              |
| Fagron                     | Prednicarbate, micronized | 160902201        | 1              |
| Euro OTC                   | Prednicarbate, micronized | 1609022-01       | 3              |
| Caelo                      | Prednicarbate, micronized | 16987410         | 1              |
| Caelo                      | Prednicarbate, micronized | 16A18-B01-322732 | 1              |
| Caelo                      | Prednicarbate, micronized | 16A18-B01-322733 | 2              |
| Fagron                     | Prednicarbate, micronized | 16E12-B01        | 2              |
| Celo                       | Prednicarbate, micronized | 1687408          | 1              |
| Fagron                     | Prednicarbate, micronized | 16E12-B01-325758 | 1              |
| Sanacorp, 01.03.17, 21,... | Prednicarbate, micronized | 1687410          | 1              |
| Fagron                     | Prednicarbate, micronized | 16E12-B01-327344 | 2              |
| Fagron                     | Prednicarbate, micronized | 16E12-B01-328270 | 1              |
| Caelo                      | Prednicarbate, micronized | 16E12-B01-325758 | 1              |
| Phoenix                    | Prednicarbate, micronized | 16J27-b01-332958 | 1              |
| Caelo                      | Prednicarbate, micronized | 17013804         | 3              |
| Fagron                     | Prednicarbate, micronized | 16J27-B01-330976 | 1              |
| Phönix                     | Prednicarbate, micronized | 16J27-B01-330976 | 1              |
| Fagron                     | Prednicarbate, micronized | 16J27-b01-330976 | 1              |
| Fagron                     | Prednicarbate, micronized | 17013804         | 1              |
| Caelo                      | Prednicarbate, micronized | 17013805         | 1              |
| Caelo                      | Prednicarbate, micronized | 17014003         | 2              |
| Caelo                      | Prednicarbate, micronized | 17014005         | 1              |
| Caelo                      | Prednicarbate, micronized | 4/AKD7           | 1              |
| Fagron                     | Prednicarbate, micronized | 701867-0001      | 1              |
| Fagron                     | Prednicarbate, micronized | NT0555M13I23-N04 | 1              |
| Fagron                     | Prednicarbate, micronized | NT0780M          | 1              |
| Fagron                     | Prednicarbate, micronized | NU0823M          | 1              |
| Fagron                     | Prednicarbate, micronized | NU0823M          | 1              |
| Fragron                    | Prednicarbate, micronized | NV0485M          | 1              |
| Fagron                     | Prednicarbate, micronized | 9E04-N02         | 1              |
| Fagron                     | Prednicarbate, micronized | 8L10-N12         | 1              |
| Fagron                     | Prednicarbate, micronized | 9G14-N06         | 1              |
| Fagron                     | Prednicarbate, micronized | 11/22-N18        | 1              |
| Fagron                     | Prednicarbate, micronized | 7061303          | 1              |
| Caelo                      | Prednicarbate, micronized | 11L23-N07        | 1              |
| Sanacorp                   | Prednicarbate, micronized | 11L23-N07        | 1              |
| Fagron                     | Prednicarbate, micronized | 11L23N07         | 1              |
| Caelo                      | Prednicarbate, micronized | 12123607         | 2              |
| Caelo                      | Prednicarbate, micronized | 12383309         | 1              |
| Caelo                      | Prednicarbate, micronized | 12383301         | 1              |
| Caelo                      | Prednicarbate, micronized | 12383304         | 2              |
| Caelo                      | Prednicarbate, micronized | 12123610         | 1              |
| Fagron                     | Prednicarbate, micronized | 12B14-N02        | 2              |
| Fagron                     | Prednicarbate, micronized | 12B20-N06        | 2              |
| Gehe                       | Prednicarbate, micronized | 12B14-N02        | 1              |
| Fagron                     | Prednicarbate, micronized | 12D27-N01        | 2              |
| Fagron                     | Prednicarbate, micronized | 12D27-N04        | 4              |
| Defektur                   | Prednicarbate, micronized | 12D27-N04        | 1              |
| Fagron                     | Prednicarbate, micronized | 12H20-No7        | 1              |
| Euro OTC                   | Prednicarbate, micronized | 1302033-02       | 2              |
| Euro OTC                   | Prednicarbate, micronized | 1302033-01       | 1              |
| Fagron                     | Prednicarbate, micronized | 13C25-N02        | 1              |
| Fagron                     | Prednicarbate, micronized | 13C25-N06        | 7              |
| Fagron                     | Prednicarbate, micronized | 13c25-no6        | 1              |
| Fagron                     | Prednicarbate, micronized | 13F11-N01        | 7              |
| Caelo                      | Prednicarbate, micronized | 13F11-N02        | 1              |
| Fagron                     | Prednicarbate, micronized | 13F11-No1        | 2              |
| Fagron                     | Prednicarbate, micronized | 13F11-N01        | 1              |

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| Supplier   | Substance                 | Batch           | Spectra |
|------------|---------------------------|-----------------|---------|
| Fagron     | Prednicarbate, micronized | 13G05-N03       | 5       |
| Gehe       | Prednicarbate, micronized | 13G05-n03       | 1       |
| Amos Vital | Prednicarbate, micronized | 13G05-N03       | 1       |
| Gehe       | Prednicarbate, micronized | 13123-N04       | 1       |
| Fagron     | Prednicarbate, micronized | 13123-N04       | 1       |
| Fagron     | Prednicarbate, micronized | 15D15-B03308161 | 1       |
| Fagron     | Prednicarbate, micronized | 12b20-n06       | 1       |
| Caelo      | Prednicarbate, micronized | 23082013A       | 1       |
| Caelo      | Prednicarbate, micronized | 1213608         | 1       |
| Fagron     | Prednicarbate, micronized | 3010E-03595     | 1       |
| Fagron     | Prednicarbate, micronized | NT0555M         | 1       |
| Caelo      | Prednicarbate, micronized | C0333/1111070   | 1       |
| Gehe       | Prednicarbate, micronized | 13372403        | 2       |
| Fagron     | Prednicarbate, micronized | 13c25-n06       | 1       |

- 69 280 spectra from 414 *Apo-Ident* customers from a total of 23 671 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Prednicarbate, micronized* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Prednicarbate, micronized* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 437           | 0              | 70 949        |
| <b>Type B</b> | 0              | 608           | 1              | 146 120       |
| <b>Type C</b> | 0              | 353           | 0              | 69 280        |

The substance/substance group *Prednicarbate, micronized* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.6270 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.8358 % (> 99.3432 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 100.0000 % (> 98.3003 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20700     | 21572               | 7.81                         | 35.69                           |
| 20832     | 20832               | 0.00                         | 29.37                           |
| 20833     | 20832               | 2.10                         | 29.44                           |
| 21368     | 21368               | 0.00                         | 28.68                           |
| 21369     | 21368               | 1.94                         | 28.80                           |
| 21572     | 21572               | 0.00                         | 32.04                           |
| 21610     | 21610               | 0.00                         | 24.81                           |
| 21858     | 21858               | 0.00                         | 25.96                           |
| 22366     | 22366               | 0.00                         | 28.95                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Prednisolon dihydrogen phosphate dinatrium</b>               |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20212-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Prednisolon dihydrogen phosphate dinatrium; Prednisoloni natrii phosphas; Prednisolonum natrii phosphoricum

### Special notes

When selecting the *Prednisolon dihydrogen phosphate dinatrium* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Prednisolon dihydrogen phosphate dinatrium*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Caelo    | Prednisolon dihy... | 13304703         | 20923     | 40      | 20130904    |
| Caelo    | Prednisolon dihy... | 13304704         | 21412     | 40      | 1411052     |
| Fagron   | Prednisolon dihy... | 14E07-B06-295251 | 21571     | 40      | 20140623    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Prednisolon dihydrogen phosphate dinatrium*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 6 reference samples from the substance/substance group *Prednisolon dihydrogen phosphate dinatrium*.

| Supplier | Substance                        | Batch            | Sample ID          | Spectra |
|----------|----------------------------------|------------------|--------------------|---------|
| Fagron   | Prednisolon dihydrogen phosph... | 11C18-N11        | 20212              | 40      |
| Caelo    | Prednisolon dihydrogen phosph... | 13304704         | 21412 <sup>†</sup> | 20      |
| Caelo    | Prednisolon dihydrogen phosph... | 13304704         | 21413              | 60      |
| Fagron   | Prednisolon dihydrogen phosph... | 14E07-B06-295251 | 21571 <sup>†</sup> | 20      |
| Fagron   | Prednisolon dihydrogen phosph... | 16I14-B03-328918 | 23270              | 40      |
| Caelo    | Prednisolon dihydrogen phosph... | 16174715         | 23271              | 40      |

- 146 509 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 53 spectra from 24 *Apo-Ident* customers from 28 batches from the substance/substance group *Prednisolon dihydrogen phosphate dinatrium*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                   | Substance                       | Batch            | Spectra |
|----------------------------|---------------------------------|------------------|---------|
| Fagron                     | Prednisolon dihydrogen phosp... | 13/27-N01        | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 13I27-N01        | 2       |
| Fagron                     | Prednisolon dihydrogen phosp... | 14E07-B06-295251 | 3       |
| Fagron                     | Prednisolon dihydrogen phosp... | 14E07-B06-295253 | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 14G30-B09        | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 14G30-B09-303012 | 7       |
| Fagron                     | Prednisolon dihydrogen phosp... | 14G30-B09-303014 | 2       |
| Caelo                      | Prednisolon dihydrogen phosp... | 15199602         | 2       |
| Caelo                      | Prednisolon dihydrogen phosp... | 15199603         | 1       |
| Caesar & Loretz GmbH Hi... | Prednisolon dihydrogen phosp... | 15C19-B05-30885  | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 15f29-b11-309694 | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 15J01-B02        | 4       |
| Fagron                     | Prednisolon dihydrogen phosp... | 15J01-B02-313610 | 2       |
| Newchem spa                | Prednisolon dihydrogen phosp... | 15J01-B02-313610 | 2       |
| Fagron                     | Prednisolon dihydrogen phosp... | 15J01-B02-317180 | 2       |
| Fagron                     | Prednisolon dihydrogen phosp... | 15K27-B09-322162 | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 15K27-B09        | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 15K27-B09-326263 | 3       |
| Alte Apotheke              | Prednisolon dihydrogen phosp... | 15K27B09-318738  | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 15K27B09-326263  | 1       |
| Caelo                      | Prednisolon dihydrogen phosp... | 16174701         | 1       |
| Caelo                      | Prednisolon dihydrogen phosp... | 16174702         | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 16I14-B03-328918 | 2       |
| Fagron                     | Prednisolon dihydrogen phosp... | 11C18-N11        | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 11K11-N11        | 2       |
| Fagron                     | Prednisolon dihydrogen phosp... | 12H30-N08        | 2       |
| Fagron                     | Prednisolon dihydrogen phosp... | 13A10-N04        | 3       |
| Fagron                     | Prednisolon dihydrogen phosp... | 13C26N06         | 1       |
| Fagron                     | Prednisolon dihydrogen phosp... | 13H19N04         | 1       |

- 69 580 spectra from 414 *Apo-Ident* customers from a total of 23 773 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Prednisolon dihydrogen phosphate dinatrium* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Prednisolon dihydrogen phosphate dinatrium* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 118           | 2              | 71 266        |
| <b>Type B</b> | 0              | 220           | 0              | 146 509       |
| <b>Type C</b> | 0              | 52            | 1              | 69 580        |

The substance/substance group *Prednisolon dihydrogen phosphate dinatrium* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 98.3333 % (> 95.8333 %)  |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.2727 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 98.1132 % (> 92.4528 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20923     | 21412               | 15.53                        | 44.23                           |
| 21412     | 21412               | 0.00                         | 40.59                           |
| 21571     | 21412               | 10.09                        | 48.71                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Prednisolone acetate</b>                                     |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20089-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Prednisolone acetate; Prednisolinum aceticum; Prednisoloni acetas

### Special notes

When selecting the *Prednisolone acetate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Prednisolone acetate*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate |
|----------|---------------------|-----------|-----------|---------|-------------|
| Caelo    | Prednisolone ace... | 12091814  | 20784     | 60      | 20120416    |
| Fagron   | Prednisolone ace... | 12H14-N07 | 20795     | 40      | 20120829    |
| Caelo    | Prednisolone ace... | 12324502  | 20877     | 20      | 20121112    |
| Euro OTC | Prednisolone ace... | 1306040   | 21096     | 40      | 20130812    |
| Caelo    | Prednisolone ace... | 13262605  | 21450     | 40      | 20130923    |

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| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------|-----------|---------|--------------------|
| Euro OTC | Prednisolone ace... | 1209028-03 | 21530     | 40      | AR-15-FG-010480-01 |
| Euro OTC | Prednisolone ace... | 1512020    | 22297     | 30      | 20160119*          |
| Fagron   | Prednisolone ace... | 12H14-N07  | 20795SI   | 34      | 20120829           |
| Caelo    | Prednisolone ace... | 13262605   | 21450SI   | 36      | 20130923           |
| Euro OTC | Prednisolone ace... | 1512020    | 22297SI   | 29      | 20160119*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 369 spectra of 10 reference samples from the substance/substance group *Prednisolone acetate*. These samples are listed above in the [calibration samples](#) section.
- 71 017 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 344 spectra of 12 reference samples from the substance/substance group *Prednisolone acetate*.

| Supplier | Substance            | Batch      | Sample ID            | Spectra |
|----------|----------------------|------------|----------------------|---------|
| Caelo    | Prednisolone acetate | 13262605   | 21448                | 60      |
| Caelo    | Prednisolone acetate | 13262605   | 21450 <sup>†</sup>   | 20      |
| Euro OTC | Prednisolone acetate | 1209028-03 | 21530 <sup>†</sup>   | 20      |
| Euro OTC | Prednisolone acetate | 1512020    | 22297 <sup>†</sup>   | 15      |
| Euro OTC | Prednisolone acetate | 1607010    | 22710                | 40      |
| Euro OTC | Prednisolone acetate | 1701041    | 23142                | 40      |
| Fagron   | Prednisolone acetate | 12H14-N07  | 20795SI <sup>†</sup> | 15      |
| Caelo    | Prednisolone acetate | 13262605   | 21448SI              | 44      |
| Caelo    | Prednisolone acetate | 13262605   | 21450SI <sup>†</sup> | 11      |
| Euro OTC | Prednisolone acetate | 1512020    | 22297SI <sup>†</sup> | 15      |
| Euro OTC | Prednisolone acetate | 1607010    | 22710SI              | 40      |
| Euro OTC | Prednisolone acetate | 1701041    | 23142SI              | 24      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146385 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 845 spectra from 256 *Apo-Ident* customers from 175 batches from the substance/substance group *Prednisolone acetate*.

| Supplier                | Substance            | Batch             | Spectra |
|-------------------------|----------------------|-------------------|---------|
| Caelo                   | Prednisolone acetate | 12324504          | 11      |
| Fagron                  | Prednisolone acetate | 12L11-B40-286915  | 3       |
| Caelo                   | Prednisolone acetate | 13262601          | 23      |
| Gutenberg-Apotheke      | Prednisolone acetate | 12L11-B40-286915  | 2       |
| VDL;7,15EUR, 21:06:14   | Prednisolone acetate | 13262602          | 1       |
| Caelo                   | Prednisolone acetate | 14175514          | 6       |
| Fiebig                  | Prednisolone acetate | 11158001          | 1       |
| Caelo                   | Prednisolone acetate | 13262609          | 5       |
| Caelo                   | Prednisolone acetate | 140601401         | 1       |
| Fagron                  | Prednisolone acetate | 13K20-B04-293970  | 2       |
| Caelo                   | Prednisolone acetate | 12091806          | 4       |
| Euro OTC                | Prednisolone acetate | 1209028-02        | 15      |
| holdermann euro         | Prednisolone acetate | 1209028-02        | 3       |
| Caelo                   | Prednisolone acetate | 12091810          | 2       |
| Caelo                   | Prednisolone acetate | 12091813          | 1       |
| Euro OTC                | Prednisolone acetate | 1306040-01        | 25      |
| Fagron                  | Prednisolone acetate | 12L05-N01         | 11      |
| Caelo                   | Prednisolone acetate | 12324509          | 3       |
| EUro/AHD                | Prednisolone acetate | 1306040-01        | 1       |
| EUro/AHD                | Prednisolone acetate | 1306040-02        | 1       |
| Fagron                  | Prednisolone acetate | 13A07-N07         | 5       |
| Fagron                  | Prednisolone acetate | 13D03-N06         | 1       |
| Phönix                  | Prednisolone acetate | 13262605          | 1       |
| Caelo                   | Prednisolone acetate | 313I-02106        | 1       |
| Euro OTC                | Prednisolone acetate | 3707556           | 1       |
| Caelo                   | Prednisolone acetate | 5031511           | 1       |
| Euro OTC                | Prednisolone acetate | 1108043-02        | 15      |
| Fagron                  | Prednisolone acetate | 115B03-B05-308582 | 1       |
| Euro OTC                | Prednisolone acetate | 1209028-03        | 2       |
| Euro OTC                | Prednisolone acetate | 1203028-03        | 1       |
| Caelo                   | Prednisolone acetate | 12091804          | 8       |
| Caelo                   | Prednisolone acetate | 12324506          | 12      |
| Caelo                   | Prednisolone acetate | 12324503          | 1       |
| Caelo                   | Prednisolone acetate | 12324508          | 11      |
| Caelo                   | Prednisolone acetate | 12324514          | 2       |
| Fagron                  | Prednisolone acetate | 12G25-N05         | 5       |
| Fagron                  | Prednisolone acetate | 12L11-B40         | 2       |
| Fagron                  | Prednisolone acetate | 12k20-b04293971   | 1       |
| Fagron                  | Prednisolone acetate | 12L11-B40-286905  | 14      |
| Phoenix                 | Prednisolone acetate | 12L11-B40-286905  | 1       |
| Euro OTC                | Prednisolone acetate | 1306040-02        | 18      |
| Symbiotica Spec./Phönix | Prednisolone acetate | 1306040-02        | 1       |

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| <b>Supplier</b>            | <b>Substance</b>     | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|----------------------|------------------|----------------|
| Caelo                      | Prednisolone acetate | 1306040-02       | 1              |
| EuRho                      | Prednisolone acetate | 1306040-03       | 1              |
| Euro OTC                   | Prednisolone acetate | 1306040-03       | 1              |
| Euro OTC                   | Prednisolone acetate | 1306040-1        | 1              |
| Euro OTC                   | Prednisolone acetate | 1306040101       | 1              |
| AHD 23.10.14 EK17,24       | Prednisolone acetate | 13262601         | 1              |
| Caelo                      | Prednisolone acetate | 13262602         | 9              |
| Caelo                      | Prednisolone acetate | 13262603         | 10             |
| Caelo                      | Prednisolone acetate | 13262605         | 15             |
| GEHE 03.07.2014            | Prednisolone acetate | 13262605         | 1              |
| Caelo                      | Prednisolone acetate | 13262606         | 5              |
| Euro OTC                   | Prednisolone acetate | 13262606         | 1              |
| Caelo                      | Prednisolone acetate | 13343112         | 1              |
| Fagron                     | Prednisolone acetate | 13K20-B04        | 2              |
| Fagron                     | Prednisolone acetate | 13K20-B04-289494 | 3              |
| Fagron                     | Prednisolone acetate | 13K20-B04-289495 | 2              |
| Fagron                     | Prednisolone acetate | 13K20-B04-293971 | 3              |
| Euro OTC                   | Prednisolone acetate | 140601-02        | 1              |
| Euro OTC                   | Prednisolone acetate | 1406012-02       | 1              |
| Euro OTC                   | Prednisolone acetate | 1406014-01       | 14             |
| Gehe                       | Prednisolone acetate | 1406014-01       | 1              |
| Lihua Pharma               | Prednisolone acetate | 1406014-01       | 1              |
| Kehr                       | Prednisolone acetate | 1406014-01       | 1              |
| Euro OTC                   | Prednisolone acetate | 1406014-02       | 14             |
| Caelo                      | Prednisolone acetate | 1406014-02       | 2              |
| Caelo                      | Prednisolone acetate | 14175508         | 15             |
| AHD 06.03.15               | Prednisolone acetate | 14175508         | 1              |
| Caelo                      | Prednisolone acetate | 14175509         | 4              |
| Cael Sanacorp 05.02.2016   | Prednisolone acetate | 14175509         | 1              |
| Caelo                      | Prednisolone acetate | 14175513         | 11             |
| Caelo                      | Prednisolone acetate | 14175512         | 1              |
| noweda                     | Prednisolone acetate | 14175513         | 1              |
| Cealo                      | Prednisolone acetate | 14175513         | 1              |
| A.H.D.                     | Prednisolone acetate | 14175514         | 1              |
| Caelo                      | Prednisolone acetate | 14380302         | 1              |
| Caelo                      | Prednisolone acetate | 14380901         | 10             |
| Cael Sanacorp 05.02.2016   | Prednisolone acetate | 14380901         | 1              |
| Caelo                      | Prednisolone acetate | 14380902         | 8              |
| Caelo                      | Prednisolone acetate | 14380905         | 12             |
| Phoenix                    | Prednisolone acetate | 14380905         | 1              |
| Caelo                      | Prednisolone acetate | 14380909         | 13             |
| sanacorp                   | Prednisolone acetate | 14380909         | 1              |
| caesar&loretz              | Prednisolone acetate | 14380909         | 1              |
| Caelo                      | Prednisolone acetate | 14380910         | 10             |
| Fagron                     | Prednisolone acetate | 14380910         | 1              |
| Wolf-Apotheke              | Prednisolone acetate | 14380911         | 1              |
| Euro OTC                   | Prednisolone acetate | 1460614-01       | 1              |
| Fagron                     | Prednisolone acetate | 14D04-B03-299294 | 2              |
| Noweda 18.05.2015          | Prednisolone acetate | 14D04-B03-299294 | 1              |
| Fagron                     | Prednisolone acetate | 14D04-B03-299295 | 1              |
| Fagron                     | Prednisolone acetate | 14D04B03299295   | 1              |
| Fagron                     | Prednisolone acetate | 14G30-B13        | 1              |
| Henan Lihua Pharmaceuti... | Prednisolone acetate | 14G30-B13        | 1              |
| Fagron                     | Prednisolone acetate | 14G30-B13-299293 | 2              |
| Fagron                     | Prednisolone acetate | 14G30-B13-302562 | 1              |
| Euro OTC                   | Prednisolone acetate |                  | 1              |
| Euro OTC                   | Prednisolone acetate | 1501036          | 1              |
| Euro OTC                   | Prednisolone acetate | 1501036-01       | 13             |
| Euro OTC                   | Prednisolone acetate | 150103601        | 1              |
| Euro OTC                   | Prednisolone acetate | 1501036-02       | 17             |

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| <b>Supplier</b>            | <b>Substance</b>     | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|----------------------|------------------|----------------|
| Euroo/Gehe                 | Prednisolone acetate | 1501036-02       | 1              |
| Caelo                      | Prednisolone acetate | 1501038-02       | 1              |
| Caelo                      | Prednisolone acetate | 15055201         | 8              |
| 15055201                   | Prednisolone acetate | 15055201         | 1              |
| Beiersdorf AG              | Prednisolone acetate | 15055201         | 1              |
| Caelo                      | Prednisolone acetate | 15055202         | 11             |
| Noweda                     | Prednisolone acetate | 15055202         | 1              |
| caesar&loretz,Phönix       | Prednisolone acetate | 15055202         | 2              |
| Caelo                      | Prednisolone acetate | 15055203         | 3              |
| Caelo                      | Prednisolone acetate | 15055206         | 7              |
| Sanacorp                   | Prednisolone acetate | 15055206         | 1              |
| Euro OTC                   | Prednisolone acetate | 1512020-01       | 25             |
| EuRho                      | Prednisolone acetate | 1512020-01       | 1              |
| Caelo                      | Prednisolone acetate | 1512020-01       | 3              |
| Euro OTC                   | Prednisolone acetate | 151202001        | 1              |
| Caelo                      | Prednisolone acetate | 151202001        | 1              |
| Caesar&Loretz GmbH         | Prednisolone acetate | 15396408         | 1              |
| Caelo                      | Prednisolone acetate | 15396304         | 1              |
| Caelo                      | Prednisolone acetate | 15398302         | 13             |
| Beiersdorf AG              | Prednisolone acetate | 15398302         | 1              |
| Caesar&Loretz,Phönix,08... | Prednisolone acetate | 15398302         | 1              |
| Caelo                      | Prednisolone acetate | 15398303         | 9              |
|                            | Prednisolone acetate | 15398303         | 1              |
| Caesar&loretz,Phoenix,2... | Prednisolone acetate |                  | 1              |
| Caelo                      | Prednisolone acetate | 15398304         | 4              |
| Phönix                     | Prednisolone acetate | 15398303         | 1              |
| Noweda                     | Prednisolone acetate | 15398303         | 1              |
| Caelo                      | Prednisolone acetate | 15398306         | 2              |
| Caesar&loretz,AHC,29.08... | Prednisolone acetate | 15398306         | 1              |
| Caelo                      | Prednisolone acetate | 15398307         | 9              |
| Caelo                      | Prednisolone acetate | 15398401         | 5              |
| Caelo                      | Prednisolone acetate | 15398402         | 6              |
| Caelo                      | Prednisolone acetate | 15398407         | 3              |
| Caelo                      | Prednisolone acetate | 15398408         | 8              |
| Caelo                      | Prednisolone acetate | 15498303         | 1              |
| Fagron                     | Prednisolone acetate | 15803-B05        | 1              |
| Fagron                     | Prednisolone acetate | 15B03-B05-302564 | 4              |
| Fagron                     | Prednisolone acetate | 15b03-b05-302564 | 1              |
| Fagron                     | Prednisolone acetate | 15B03-B05-302566 | 3              |
| Fagron                     | Prednisolone acetate | 15B03-B05-308582 | 1              |
| Euro OTC                   | Prednisolone acetate | 1607010-01       | 35             |
| Caelo                      | Prednisolone acetate | 16/AKD2          | 1              |
| Caelo                      | Prednisolone acetate | 160701001        | 1              |
| Caelo                      | Prednisolone acetate | 16246801         | 5              |
| Caelo                      | Prednisolone acetate | 16246802         | 3              |
| Caelo                      | Prednisolone acetate | 16246803         | 4              |
| Caesar&LoretzGmbH,11.03... | Prednisolone acetate | 16246803         | 1              |
| Gehe                       | Prednisolone acetate | 16246803         | 2              |
| Caelo                      | Prednisolone acetate | 16246804         | 4              |
| Gehe                       | Prednisolone acetate | 16246806         | 1              |
| Caelo                      | Prednisolone acetate | 16246806         | 2              |
| Caelo                      | Prednisolone acetate | 16246807         | 3              |
| Caelo                      | Prednisolone acetate | 16246808         | 2              |
| Caelo                      | Prednisolone acetate | 16246809         | 1              |
| Caelo                      | Prednisolone acetate | 16246811         | 1              |
| Caelo                      | Prednisolone acetate | 1624806          | 1              |
| Caelo                      | Prednisolone acetate | 165246802        | 1              |
| Euro OTC                   | Prednisolone acetate | 1701041-01       | 2              |
| Caesar&Loretz GmbH,PHön... | Prednisolone acetate | 17086103         | 2              |
| Caesar & Loretz GmbH, P... | Prednisolone acetate | 17185601         | 1              |

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| <b>Supplier</b>     | <b>Substance</b>     | <b>Batch</b>  | <b>Spectra</b> |
|---------------------|----------------------|---------------|----------------|
| Caelo               | Prednisolone acetate | 17086103      | 1              |
| Bombastus           | Prednisolone acetate | 2255          | 1              |
| Fagron              | Prednisolone acetate | 200540-0013   | 1              |
| Euro OTC            | Prednisolone acetate | 2215I-02106   | 1              |
| Euro OTC            | Prednisolone acetate | 2714U-02106   | 1              |
| Euro OTC            | Prednisolone acetate | 289295        | 1              |
| Euro OTC            | Prednisolone acetate | 5012I-02106   | 1              |
| Fagron              | Prednisolone acetate | K07A20131101M | 1              |
| Fagron              | Prednisolone acetate | K07D20150105M | 1              |
| Fagron              | Prednisolone acetate | K07A20130903M | 1              |
| Euro OTC            | Prednisolone acetate | 514U2106      | 1              |
| Fagron              | Prednisolone acetate | 113Q-02106    | 1              |
| Fagron              | Prednisolone acetate | 6082013D      | 2              |
| Euro OTC            | Prednisolone acetate | 711212106     | 1              |
| Caelo               | Prednisolone acetate | 11080403      | 1              |
| Euro OTC            | Prednisolone acetate | 1108043-01    | 4              |
| Caelo               | Prednisolone acetate | 6021306       | 1              |
| EuRho/G             | Prednisolone acetate | 1108043-02    | 1              |
| Caelo               | Prednisolone acetate | 11158002      | 1              |
| Phoenix             | Prednisolone acetate | 11158007      | 1              |
| Caelo               | Prednisolone acetate | 11158007      | 1              |
| Caelo               | Prednisolone acetate | 11158003      | 1              |
| Noweda              | Prednisolone acetate | 11I09-N08     | 1              |
| Phönix              | Prednisolone acetate | 11158008      | 1              |
| Kehr                | Prednisolone acetate | 1158007       | 1              |
| Fagron              | Prednisolone acetate | 11A31-N03     | 1              |
| Fagron              | Prednisolone acetate | 11I09-N08     | 1              |
| Fagron              | Prednisolone acetate | 11L21-N03     | 1              |
| Fagron              | Prednisolone acetate | 11I09N-08     | 1              |
| Caelo               | Prednisolone acetate | 11L21-N03     | 2              |
| Fargo               | Prednisolone acetate | 12025-N05     | 1              |
| Euro OTC            | Prednisolone acetate | 1209028-01    | 4              |
| Caelo               | Prednisolone acetate | 1209028-01    | 2              |
| Noweda              | Prednisolone acetate | 1209028-01    | 1              |
| Caelo               | Prednisolone acetate | 1209028-02    | 2              |
| Phönix              | Prednisolone acetate | 1209028-02    | 1              |
| Gehe                | Prednisolone acetate | 1209028-02    | 1              |
| Caelo               | Prednisolone acetate | 12091802      | 8              |
| Anzag, 24.10.2012   | Prednisolone acetate | 12091802      | 1              |
| ANZAG               | Prednisolone acetate | 12091802      | 2              |
| Caelo               | Prednisolone acetate | 12091803      | 6              |
| Fagron              | Prednisolone acetate | 12091803      | 1              |
| Caelo               | Prednisolone acetate | 12091807      | 7              |
| Alliance Healthcare | Prednisolone acetate | 12091807      | 1              |
| Caelo               | Prednisolone acetate | 12091808      | 4              |
| Sanacorp            | Prednisolone acetate | 12091808      | 1              |
| Anzag 01.02.2013    | Prednisolone acetate | 12091813      | 1              |
| Caelo               | Prednisolone acetate | 12091814      | 7              |
| Caelo               | Prednisolone acetate | 12091815      | 2              |
| Caelo               | Prednisolone acetate | 12324502      | 15             |
| Fagron              | Prednisolone acetate | 12324502      | 1              |
| Caelo               | Prednisolone acetate | 12324505      | 16             |
| Phönix              | Prednisolone acetate | 12324505      | 1              |
| Phönix              | Prednisolone acetate | 12324506      | 1              |
| Noweda              | Prednisolone acetate | 12324506      | 1              |
| AHD, 08.11.13       | Prednisolone acetate | 12324506      | 1              |
| Caelo               | Prednisolone acetate | 1234502       | 1              |
| Fagron              | Prednisolone acetate | 12C19-N03     | 3              |
| Caelo               | Prednisolone acetate | 1234506       | 2              |
| Fagron              | Prednisolone acetate | 12C19-N03     | 1              |

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| Supplier                  | Substance            | Batch            | Spectra |
|---------------------------|----------------------|------------------|---------|
| FARGON                    | Prednisolone acetate | 12g25-n05        | 1       |
| Fagron                    | Prednisolone acetate | 12H14-N07        | 3       |
| Gehe                      | Prednisolone acetate | 12H14-N07        | 1       |
| Fagron                    | Prednisolone acetate | 12J10/N05        | 1       |
| Fagron                    | Prednisolone acetate | 12J10-N05        | 1       |
| FARGON                    | Prednisolone acetate | 12105-n01        | 1       |
| Fagron                    | Prednisolone acetate | 12L11-B04-286905 | 1       |
| Symbiotika/Anzag          | Prednisolone acetate | 1306040-01       | 1       |
| Caelo                     | Prednisolone acetate | 1306040-01       | 1       |
| Euro OTC                  | Prednisolone acetate | 130604002        | 1       |
| Caesar&lloretz,Phoenix    | Prednisolone acetate | 13262606         | 1       |
| Anzag                     | Prednisolone acetate | 13A07N07         | 1       |
| Fagron                    | Prednisolone acetate | 13a07n07         | 1       |
| Caelo                     | Prednisolone acetate | 13A07-N07        | 2       |
| A.H. 23.05.13 ek: 5,40EUR | Prednisolone acetate | 13A07-N07        | 1       |
| Fargon                    | Prednisolone acetate | 13A07-N07        | 1       |
| Caelo                     | Prednisolone acetate |                  | 2       |
| Caesar&lloretz,Phoenix    | Prednisolone acetate | 14175513         | 1       |
| apo-ident                 | Prednisolone acetate | 1512020-01       | 1       |
| Fagron                    | Prednisolone acetate | 180713a          | 1       |
| Caelo                     | Prednisolone acetate | 1616I-02106      | 1       |
| Euro OTC                  | Prednisolone acetate | 2413Q02106       | 1       |
| Euro OTC                  | Prednisolone acetate | 200540           | 1       |
| Euro OTC                  | Prednisolone acetate | 2507212106       | 1       |
| Caelo                     | Prednisolone acetate | 27051301         | 1       |
| Euro OTC                  | Prednisolone acetate | 2902212106       | 1       |
| Caelo                     | Prednisolone acetate | 4313A-02106      | 1       |
| Euro OTC                  | Prednisolone acetate | PAC-BLT003/0812  | 1       |
| Euro OTC                  | Prednisolone acetate | K07A20140304M    | 1       |
| Gehe                      | Prednisolone acetate | 13262609         | 1       |
| Fagron                    | Prednisolone acetate | 12H14-N07        | 1       |

- 68 788 spectra from 413 *Apo-Ident* customers from a total of 23 632 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Prednisolone acetate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Prednisolone acetate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 369           | 0              | 71 017        |
| <b>Type B</b> | 0              | 344           | 0              | 146 385       |
| <b>Type C</b> | 0              | 793           | 52             | 68 788        |

The substance/substance group *Prednisolone acetate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.3740 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.2558 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 93.8462 % (> 93.4911 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20784     | 22297               | 8.96                         | 40.52                           |
| 20795     | 22297               | 8.48                         | 33.10                           |
| 20877     | 22297               | 5.17                         | 43.32                           |
| 21096     | 22297               | 7.96                         | 34.50                           |
| 21450     | 22297               | 13.06                        | 37.92                           |
| 21530     | 21530               | 0.00                         | 38.41                           |
| 22297     | 22297               | 0.00                         | 44.93                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Prednisolone hydrogen succinate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20838-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Prednisolone hydrogen succinate; Prednisoloni hydrogenosuccinas

### Special notes

When selecting the *Prednisolone hydrogen succinate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Prednisolone hydrogen succinate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Prednisolone hyd... | 12A20-N11        | 20838     | 40      | 20120126    |
| Fagron   | Prednisolone hyd... | 13D16-N11        | 20956     | 40      | 1509250     |
| Fagron   | Prednisolone hyd... | 14G29-B07-304733 | 22652     | 40      | 1701370     |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Prednisolone hydrogen succinate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 40 spectra of 1 reference samples from the substance/substance group *Prednisolone hydrogen succinate*.

| Supplier | Substance                       | Batch            | Sample ID | Spectra |
|----------|---------------------------------|------------------|-----------|---------|
| Fagron   | Prednisolone hydrogen succin... | 14G29-B07-304733 | 22723     | 40      |

- 146 689 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 6 spectra from 4 *Apo-Ident* customers from 6 batches from the substance/substance group *Prednisolone hydrogen succinate*.

| Supplier | Substance                       | Batch            | Spectra |
|----------|---------------------------------|------------------|---------|
| Caelo    | Prednisolone hydrogen succin... | 12A20-N11        | 1       |
| Phönix   | Prednisolone hydrogen succin... | 13H24-N04        | 1       |
| Fagron   | Prednisolone hydrogen succin... | 14G29-B07        | 1       |
| Fagron   | Prednisolone hydrogen succin... | 14G29-B07-304733 | 1       |
| Caelo    | Prednisolone hydrogen succin... | 15C11-B05-305533 | 1       |
| Caelo    | Prednisolone hydrogen succin... | 19081502         | 1       |

- 69 627 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Prednisolone hydrogen succinate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Prednisolone hydrogen succinate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 40            | 0              | 146 689       |
| <b>Type C</b> | 0              | 6             | 0              | 69 627        |

The substance/substance group *Prednisolone hydrogen succinate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 85.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8815 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20838     | 22652               | 6.82                         | 33.65                           |
| 20956     | 20956               | 0.00                         | 35.13                           |
| 22652     | 22652               | 0.00                         | 32.86                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Labor-

prüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Prednisolone, micronized**  
 Substance class APIs & excipients, solid  
 Report date 19/01/2018  
 Report number 20773-2018-01-19  
 Executing company HiperScan GmbH  
 Weißeritzstraße 3  
 01067 Dresden  
 Germany

### Relevant substance names

Prednisolone, micronized; Prednisolonum micronisatum

### Special notes

When selecting the *Prednisolone, micronized* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
 Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
 AA004 *Erstellung und Validierung eines IdentModul-Updates*  
 Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Prednisolone, micronized*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Caelo    | Prednisolone, mi... | 12324202         | 20773     | 40      | 20121113    |
| Caelo    | Prednisolone, mi... | 12324226         | 21303     | 39      | 1411271     |
| Caelo    | Prednisolone, mi... | 13343105         | 21449     | 40      | 1411232     |
| Euro OTC | Prednisolone, mi... | 1212021-02       | 21604     | 40      | 1411270     |
| Fagron   | Prednisolone, mi... | 13H07-B02-285592 | 21660     | 40      | 20130909    |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Euro OTC | Prednisolone, mi... | 1501047-01       | 21849     | 40      | AR-15-FG-015509-01 |
| Caelo    | Prednisolone, mi... | 154000           | 22435     | 40      | 20160225*          |
| Caelo    | Prednisolone, mi... | 161343           | 22467     | 40      | 20160601*          |
| Fagron   | Prednisolone, mi... | 14I10-B03-302263 | 22651     | 40      | 20141020           |
| Euro OTC | Prednisolone, mi... | 1607011          | 22709     | 40      | 20160818*          |
| Caelo    | Prednisolone, mi... | 15400002         | 22783     | 40      | 20160225           |
| Fagron   | Prednisolone, mi... | 16C15-B01-320761 | 22803     | 40      | 20160407           |
| Euro OTC | Prednisolone, mi... | 1212021-02       | 21604SI   | 33      | 1411270            |
| Fagron   | Prednisolone, mi... | 13H07-B02-285592 | 21660SI   | 40      | 20130909           |
| Euro OTC | Prednisolone, mi... | 1501047-01       | 21849SI   | 20      | AR-15-FG-015509-01 |
| Caelo    | Prednisolone, mi... | 154000           | 22435SI   | 39      | 20160225*          |
| Caelo    | Prednisolone, mi... | 161343           | 22467SI   | 32      | 20160601*          |
| Fagron   | Prednisolone, mi... | 14I10-B03-302263 | 22651SI   | 40      | 20141020           |
| Euro OTC | Prednisolone, mi... | 1607011          | 22709SI   | 40      | 20160818*          |
| Caelo    | Prednisolone, mi... | 15400002         | 22783SI   | 40      | 20160225           |
| Fagron   | Prednisolone, mi... | 16C15-B01-320761 | 22803SI   | 36      | 20160407           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 799 spectra of 21 reference samples from the substance/substance group *Prednisolone, micronized*. These samples are listed above in the [calibration samples](#) section.
- 70 587 spectra from a total of 1540 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 521 spectra of 20 reference samples from the substance/substance group *Prednisolone, micronized*.

| Supplier | Substance                | Batch      | Sample ID | Spectra |
|----------|--------------------------|------------|-----------|---------|
| Caelo    | Prednisolone, micronized | 81798119   | 20023     | 50      |
| Fagron   | Prednisolone, micronized | 1108055-04 | 20855     | 30      |
| Fagron   | Prednisolone, micronized | pending    | 21008     | 30      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

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| Supplier | Substance                | Batch            | Sample ID            | Spectra |
|----------|--------------------------|------------------|----------------------|---------|
| Fagron   | Prednisolone, micronized | 9K05-N02         | 21019                | 30      |
| Caelo    | Prednisolone, micronized | 13343105         | 21449 <sup>†</sup>   | 20      |
| Euro OTC | Prednisolone, micronized | 1212021-02       | 21604 <sup>†</sup>   | 20      |
| Fagron   | Prednisolone, micronized | 13H07-B02-285592 | 21660 <sup>†</sup>   | 20      |
| Euro OTC | Prednisolone, micronized | 1501047-01       | 21849 <sup>†</sup>   | 20      |
| Caelo    | Prednisolone, micronized | 154000           | 22435 <sup>†</sup>   | 20      |
| Caelo    | Prednisolone, micronized | 161343           | 22467 <sup>†</sup>   | 20      |
| Euro OTC | Prednisolone, micronized | 1702020          | 23180                | 40      |
| Fagron   | Prednisolone, micronized | 16E09-B07-328220 | 23260                | 40      |
| Caelo    | Prednisolone, micronized | 13343105         | 21451SI              | 60      |
| Euro OTC | Prednisolone, micronized | 1212021-02       | 21604SI <sup>†</sup> | 15      |
| Fagron   | Prednisolone, micronized | 13H07-B02-285592 | 21660SI <sup>†</sup> | 20      |
| Euro OTC | Prednisolone, micronized | 1501047-01       | 21849SI <sup>†</sup> | 10      |
| Caelo    | Prednisolone, micronized | 154000           | 22435SI <sup>†</sup> | 20      |
| Caelo    | Prednisolone, micronized | 161343           | 22467SI <sup>†</sup> | 15      |
| Euro OTC | Prednisolone, micronized | 1702020          | 23180SI              | 21      |
| Fagron   | Prednisolone, micronized | 16E09-B07-328220 | 23260SI              | 20      |

- 146 208 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 746 spectra from 250 *Apo-Ident* customers from 186 batches from the substance/substance group *Prednisolone, micronized*.

| Supplier              | Substance                | Batch      | Spectra |
|-----------------------|--------------------------|------------|---------|
| Euro OTC              | Prednisolone, micronized | 1108055-04 | 25      |
| Euro OTC              | Prednisolone, micronized | 501047-01  | 1       |
| Caelo                 | Prednisolone, micronized | 10196606   | 1       |
| Caelo                 | Prednisolone, micronized | 10196626   | 7       |
| Fagron                | Prednisolone, micronized | 613Q-02105 | 1       |
| Euro OTC              | Prednisolone, micronized | 110805502  | 1       |
| Euro OTC              | Prednisolone, micronized | 1212021-01 | 27      |
| Euro OTC              | Prednisolone, micronized | 1212021    | 1       |
| Euro OTC              | Prednisolone, micronized | 121021-01  | 2       |
| Caelo                 | Prednisolone, micronized | 1212021-01 | 1       |
| Euro OTC              | Prednisolone, micronized | 121202101  | 1       |
| euroct/gehe           | Prednisolone, micronized | 1212021-01 | 2       |
| Gehe                  | Prednisolone, micronized | 1212021-01 | 4       |
| Tianyao Pharma/Phönix | Prednisolone, micronized | 1212021-01 | 1       |
| Euro OTC              | Prednisolone, micronized | 1212021-02 | 23      |
| Caelo                 | Prednisolone, micronized | 121202102  | 1       |
| Euro OTC              | Prednisolone, micronized | 121202102  | 1       |
| Euro OTC              | Prednisolone, micronized | 1212021-03 | 20      |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier                 | Substance                | Batch            | Spectra |
|--------------------------|--------------------------|------------------|---------|
| Caelo                    | Prednisolone, micronized | 1212021-03       | 4       |
| AHD                      | Prednisolone, micronized | 121202103        | 1       |
| Euro/ Sanacorp           | Prednisolone, micronized | 121202103        | 1       |
| Caelo                    | Prednisolone, micronized | 12324217         | 7       |
| Caelo                    | Prednisolone, micronized | 12324220         | 2       |
| Caelo                    | Prednisolone, micronized | 12324226         | 10      |
| Caelo                    | Prednisolone, micronized | 12324213         | 7       |
| Caelo                    | Prednisolone, micronized | 12324221         | 4       |
| Caelo                    | Prednisolone, micronized | 1234556          | 1       |
| Euro OTC                 | Prednisolone, micronized | 1314Q2105        | 1       |
| Caelo                    | Prednisolone, micronized | 13343101         | 1       |
| Caelo                    | Prednisolone, micronized | 133414           | 1       |
| Caelo                    | Prednisolone, micronized | 13343104         | 8       |
| Caelo                    | Prednisolone, micronized | 13343105         | 6       |
| Phönix Gotha             | Prednisolone, micronized | 13343105         | 1       |
| Caelo                    | Prednisolone, micronized | 13343106         | 8       |
| Euro OTC                 | Prednisolone, micronized | 13343104         | 1       |
| Fagron                   | Prednisolone, micronized | 13343106         | 1       |
| Caelo                    | Prednisolone, micronized | 13343107         | 2       |
| Gehe                     | Prednisolone, micronized | 13343107         | 1       |
| Caelo                    | Prednisolone, micronized | 13343111         | 4       |
| Phönix Gotha             | Prednisolone, micronized | 13343111         | 1       |
| Phönix Gotha             | Prednisolone, micronized | 13343112         | 2       |
| Caelo                    | Prednisolone, micronized | 13343112         | 1       |
| Caesar&Loretz GmbH/Anzag | Prednisolone, micronized | 13343112         | 1       |
| Caelo                    | Prednisolone, micronized | 13343113         | 2       |
| Caelo                    | Prednisolone, micronized | 13343114         | 5       |
| Caelo                    | Prednisolone, micronized | 13343115         | 9       |
| Berkel AHK               | Prednisolone, micronized | 13343115         | 1       |
| Caelo                    | Prednisolone, micronized | 13343116         | 4       |
| Fagron                   | Prednisolone, micronized | 13A07N14         | 1       |
| Fagron                   | Prednisolone, micronized | 13A07-N14        | 8       |
| Fagron                   | Prednisolone, micronized | 13E15-N06        | 16      |
| Fagron                   | Prednisolone, micronized | 13E13-N06        | 1       |
| Fagron                   | Prednisolone, micronized | 13H07-B02        | 1       |
| Fagron                   | Prednisolone, micronized | 13H07-B020       | 1       |
| Caelo                    | Prednisolone, micronized | 13H07-B02-285590 | 1       |
| Fagron                   | Prednisolone, micronized | 13G03-B09-289668 | 1       |
| Fagron                   | Prednisolone, micronized | 13H07-B02-285592 | 3       |
| Fagron                   | Prednisolone, micronized | 13H07-B02-285590 | 1       |
| Fagron                   | Prednisolone, micronized | 13H07-B02-285593 | 4       |
| Fagron                   | Prednisolone, micronized | 13H07-B02-285593 | 1       |
| Fagron                   | Prednisolone, micronized | 13J28-B06        | 1       |
| Fagron                   | Prednisolone, micronized | 13J28-B06-289670 | 3       |
| Sanacorp                 | Prednisolone, micronized | 13j28-b06-289670 | 1       |
| Fagron                   | Prednisolone, micronized | 14/10-B03        | 1       |
| Fagron                   | Prednisolone, micronized |                  | 2       |
| Fagron                   | Prednisolone, micronized | 14/10-B03-302265 | 3       |
| Caelo                    | Prednisolone, micronized | 14/10B03302265   | 1       |
| Fagron                   | Prednisolone, micronized | 14/10B03302265   | 1       |
| Fagron                   | Prednisolone, micronized | 14/10-B03-302266 | 2       |
| Fagron                   | Prednisolone, micronized | 14/10-B03-302269 | 1       |
| Fagron                   | Prednisolone, micronized | 1410-B03         | 1       |
| Fagron                   | Prednisolone, micronized | 1410-B03-302269  | 1       |
| Fagron                   | Prednisolone, micronized | 14A30-B02-294968 | 4       |
| Fischer/Gehe             | Prednisolone, micronized | 14A30-B02-294968 | 1       |
| Caelo                    | Prednisolone, micronized | 14A30-B02-294968 | 1       |
| Phönix                   | Prednisolone, micronized | 14B18-B05-294966 | 1       |
| Fagron                   | Prednisolone, micronized | 14B18-B05-294966 | 8       |
| Caelo                    | Prednisolone, micronized | 14B18-B05-294966 | 2       |

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| Supplier             | Substance                | Batch            | Spectra |
|----------------------|--------------------------|------------------|---------|
| Fagron               | Prednisolone, micronized | 14B18-B05294966  | 1       |
| Fagron               | Prednisolone, micronized | 14B18-B05-294969 | 2       |
| Fagron               | Prednisolone, micronized | 14B18-B05-294966 | 1       |
| Fagron               | Prednisolone, micronized | 14G30-B14        | 1       |
| Caelo                | Prednisolone, micronized | 14G30-B14-302262 | 1       |
| Fagron               | Prednisolone, micronized | 14G30-B14-302262 | 4       |
| Fagron               | Prednisolone, micronized | 14I10-B03        | 2       |
| Fagron               | Prednisolone, micronized | 14I10-B03-302266 | 1       |
| Fagron               | Prednisolone, micronized | 14L10-B03-302269 | 1       |
| Fagron               | Prednisolone, micronized | 14I10-B03-302269 | 1       |
| Fagron               | Prednisolone, micronized | 14i10-b03-302269 | 1       |
| Euro OTC             | Prednisolone, micronized | 1501047-01       | 11      |
| Euro OTC             | Prednisolone, micronized | 1501047          | 1       |
| Euro OTC             | Prednisolone, micronized | 150104701        | 2       |
| Caelo                | Prednisolone, micronized | 1501047-01       | 2       |
| Caelo                | Prednisolone, micronized | 150104701        | 1       |
| Bombastus            | Prednisolone, micronized | 1501047-02       | 1       |
| Euro OTC             | Prednisolone, micronized | 1501047-02       | 6       |
| Henan Lihua/Gehe     | Prednisolone, micronized | 1501047-01       | 1       |
| Caelo                | Prednisolone, micronized | 15055101         | 3       |
| Euro OTC             | Prednisolone, micronized | 150104747-01     | 1       |
| Caelo                | Prednisolone, micronized | 15055102         | 5       |
| Caelo                | Prednisolone, micronized | 15206101         | 8       |
| Caesar & Loretz GmbH | Prednisolone, micronized | 15206101         | 3       |
| Caelo                | Prednisolone, micronized | 152006105        | 1       |
| Caelo                | Prednisolone, micronized | 15206102         | 11      |
| Noweda               | Prednisolone, micronized | 15206101         | 1       |
| Caelo                | Prednisolone, micronized | 15206103         | 11      |
| Caelo                | Prednisolone, micronized | 15206105         | 5       |
| Caelo                | Prednisolone, micronized | 15206108         | 8       |
| Caelo                | Prednisolone, micronized | 15400002         | 7       |
| Phoenix              | Prednisolone, micronized | 15400003         | 1       |
| Caelo                | Prednisolone, micronized | 15400003         | 12      |
| Caelo                | Prednisolone, micronized | 15400004         | 7       |
| Caelo                | Prednisolone, micronized | 15400010         | 1       |
| Caelo                | Prednisolone, micronized | 1540003          | 1       |
| Fagron               | Prednisolone, micronized | 15D14-B01-308425 | 2       |
| Fagron               | Prednisolone, micronized | 15K03-B04        | 1       |
| Sanacorp             | Prednisolone, micronized | 15K03-B04-314226 | 1       |
| Fagron               | Prednisolone, micronized | 15K03-B04-314226 | 3       |
| Fagron               | Prednisolone, micronized | 15K03B04314226   | 1       |
| Fragon/Phoenix       | Prednisolone, micronized | 15K03-B04-314226 | 1       |
| Fagron               | Prednisolone, micronized | 15k03-b04-314226 | 2       |
| Fagron               | Prednisolone, micronized | 15K03-B04-314358 | 3       |
| Caelo                | Prednisolone, micronized | 15K03-B04-314358 | 1       |
| Fagron               | Prednisolone, micronized | 15K03-B04-314869 | 1       |
| Euro OTC             | Prednisolone, micronized | 1607011-01       | 7       |
| Caelo                | Prednisolone, micronized | 16134301         | 4       |
| AHD                  | Prednisolone, micronized | 160711-01        | 1       |
| Caelo                | Prednisolone, micronized | 16134302         | 1       |
| Gehe                 | Prednisolone, micronized | 16134302         | 1       |
| Caelo                | Prednisolone, micronized | 16134305         | 2       |
| Fagron               | Prednisolone, micronized | 16A20-B03        | 3       |
| Fagron               | Prednisolone, micronized | 16A20-B03-316420 | 1       |
| Fagron               | Prednisolone, micronized | 16A20-B03-316421 | 1       |
| Fagron               | Prednisolone, micronized | 16A20-B03-319015 | 1       |
| Fagron               | Prednisolone, micronized | 16C15-B01        | 1       |
| Caelo                | Prednisolone, micronized | 16C15-B01320761  | 1       |
| Fagron               | Prednisolone, micronized | 16c15-B01-320761 | 1       |
| Caelo                | Prednisolone, micronized | 16C15-B01-321979 | 1       |

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| Supplier                   | Substance                | Batch            | Spectra |
|----------------------------|--------------------------|------------------|---------|
| Fagron                     | Prednisolone, micronized | 16C15-B01-320761 | 1       |
| Caelo                      | Prednisolone, micronized | 16C15-B01-320761 | 1       |
| Fagron                     | Prednisolone, micronized | 16C15-B01-321979 | 1       |
| Fagron                     | Prednisolone, micronized | 16C15-B02-324943 | 2       |
| Caelo                      | Prednisolone, micronized | 19081504         | 1       |
| Euro OTC                   | Prednisolone, micronized | 30042014B        | 1       |
| Caelo                      | Prednisolone, micronized | 4712I-02105      | 1       |
| Caelo                      | Prednisolone, micronized |                  | 1       |
| Caelo                      | Prednisolone, micronized | k04c20121219     | 1       |
| Fagron                     | Prednisolone, micronized | K04C20130203M    | 1       |
| Fagron                     | Prednisolone, micronized | K04C20140502     | 1       |
| Caelo                      | Prednisolone, micronized | P142/14          | 1       |
| Fagron                     | Prednisolone, micronized | K04C20121006     | 1       |
| Caelo                      | Prednisolone, micronized | 10196611         | 3       |
| Caelo                      | Prednisolone, micronized | 10196614         | 1       |
| EuRho                      | Prednisolone, micronized | 1012012-02       | 2       |
| Caelo                      | Prednisolone, micronized | 1012012-02       | 1       |
| EuRho                      | Prednisolone, micronized | 1012012-01       | 1       |
| Caelo                      | Prednisolone, micronized | 9244213          | 1       |
| Kehr                       | Prednisolone, micronized | 10196622         | 1       |
| Caelo                      | Prednisolone, micronized | 10196622         | 2       |
| Caelo                      | Prednisolone, micronized | 10196623         | 1       |
| Phönix Gotha               | Prednisolone, micronized | 10196626         | 2       |
| Caelo                      | Prednisolone, micronized | 10196625         | 1       |
| Caelo                      | Prednisolone, micronized | 10196627         | 11      |
| Caelo                      | Prednisolone, micronized | 11/26-N04        | 1       |
| Euro OTC                   | Prednisolone, micronized | 1108055-02       | 5       |
| Euro OTC                   | Prednisolone, micronized | 1108055-03       | 12      |
| Fagron                     | Prednisolone, micronized | 11D13-N05        | 1       |
| Fagron                     | Prednisolone, micronized | 11G22-N08        | 2       |
| Fagron                     | Prednisolone, micronized | 11J26-N04        | 3       |
| Caelo                      | Prednisolone, micronized | 12171301         | 6       |
| Phoenix                    | Prednisolone, micronized | 11j26-N04        | 2       |
| Fagron                     | Prednisolone, micronized | 12C22-N05        | 8       |
| Noweda                     | Prednisolone, micronized | 12C22-N05        | 1       |
| Gehe                       | Prednisolone, micronized | 12C22-N05        | 1       |
| A.H. 05.03.13 ek: 14,08EUR | Prednisolone, micronized | 12D30-N04        | 1       |
| Caelo                      | Prednisolone, micronized | 9193501          | 1       |
| europharma                 | Prednisolone, micronized | 1002001240       | 1       |
| Alliance Health 04.01.2... | Prednisolone, micronized | 1012012-01       | 1       |
| Caelo                      | Prednisolone, micronized | 1511011          | 1       |
| Noweda                     | Prednisolone, micronized | 9244213          | 1       |
| Euro OTC                   | Prednisolone, micronized | 1012012-02       | 2       |
| Caelo                      | Prednisolone, micronized | 1012012-01       | 1       |
| Caelo                      | Prednisolone, micronized | 10196604         | 1       |
| Caelo                      | Prednisolone, micronized | 1019611          | 1       |
| Caelo                      | Prednisolone, micronized | 10196619         | 1       |
| Noweda                     | Prednisolone, micronized | 10196626         | 2       |
| Sanacorp                   | Prednisolone, micronized | 1108055-03       | 1       |
| Euro OTC                   | Prednisolone, micronized | 1108055-01       | 1       |
| Euopharm/Otto              | Prednisolone, micronized | 1108055-03       | 1       |
| EuRho                      | Prednisolone, micronized | 1108055-03       | 2       |
| Euopharm/Otto              | Prednisolone, micronized | 1108055-04       | 5       |
| Euro OTC                   | Prednisolone, micronized | 110805504        | 6       |
| EuRho/Jenne                | Prednisolone, micronized | 1108055-04       | 2       |
| Apotheke Mildenau          | Prednisolone, micronized | 1108055-04       | 3       |
| Caelo                      | Prednisolone, micronized | 1108055-04       | 1       |
| Sanacorp                   | Prednisolone, micronized | 110805504        | 1       |
| Euro OTC                   | Prednisolone, micronized | 110855-02        | 1       |
| Euro OTC                   | Prednisolone, micronized | 118055-04        | 1       |

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| <b>Supplier</b>          | <b>Substance</b>         | <b>Batch</b> | <b>Spectra</b> |
|--------------------------|--------------------------|--------------|----------------|
| Sanacorp                 | Prednisolone, micronized | 1212021      | 1              |
| Caelo                    | Prednisolone, micronized | 12171302     | 1              |
| Gehe                     | Prednisolone, micronized | 12171302     | 1              |
| Anzag 15.10.12           | Prednisolone, micronized | 12171303     | 1              |
| Caelo                    | Prednisolone, micronized | 12171303     | 3              |
| Phoenix, 03.09.2012      | Prednisolone, micronized | 12185702     | 1              |
| Caelo                    | Prednisolone, micronized | 12171306     | 2              |
| Phönix Gotha             | Prednisolone, micronized | 12185702     | 1              |
| Caelo                    | Prednisolone, micronized | 12185702     | 2              |
| Fagron                   | Prednisolone, micronized | 12324202     | 1              |
| Caelo                    | Prednisolone, micronized | 12324202     | 11             |
| Phönix Gotha             | Prednisolone, micronized | 1232417      | 1              |
| Caelo                    | Prednisolone, micronized | 1232417      | 1              |
| Caelo                    | Prednisolone, micronized | 12324203     | 6              |
| Phönix Gotha             | Prednisolone, micronized | 12324204     | 1              |
| Caelo                    | Prednisolone, micronized | 12324204     | 4              |
| Caesar/Lorenz            | Prednisolone, micronized | 12324204     | 1              |
| Caelo                    | Prednisolone, micronized | 12324205     | 15             |
| Caelo                    | Prednisolone, micronized | 12324207     | 4              |
| Phönix Gotha             | Prednisolone, micronized | 12324207     | 1              |
| Caelo                    | Prednisolone, micronized | 12324206     | 1              |
| Caesar & Loretz GmbH     | Prednisolone, micronized | 12324205     | 1              |
| Gehe 03.07.2013          | Prednisolone, micronized | 12324207     | 1              |
| Phönix Gotha             | Prednisolone, micronized | 12324213     | 1              |
| Caelo                    | Prednisolone, micronized | 12324216     | 15             |
| Phönix                   | Prednisolone, micronized | 12324216     | 1              |
| Phönix Gotha             | Prednisolone, micronized | 12324217     | 1              |
| Gehe                     | Prednisolone, micronized | 12324219     | 2              |
| Caelo                    | Prednisolone, micronized | 12324219     | 11             |
| Sonnenberg-Apotheke      | Prednisolone, micronized | 12324219     | 1              |
| Caesar & Loretz GmbH     | Prednisolone, micronized | 12324219     | 1              |
| Caelo                    | Prednisolone, micronized | 123242216    | 1              |
| Caelo                    | Prednisolone, micronized | 1234205      | 1              |
| Fagron                   | Prednisolone, micronized | 12D30N04     | 1              |
| Fagron                   | Prednisolone, micronized | 12C22N05     | 1              |
| FARGON                   | Prednisolone, micronized | 12c22-n05    | 1              |
| Fagron                   | Prednisolone, micronized | 12c22-N05    | 2              |
| Fagron                   | Prednisolone, micronized | 12D30-N04    | 10             |
| Fargon/19.07.2013/Noweda | Prednisolone, micronized | 12D30-N04    | 2              |
| Fargo                    | Prednisolone, micronized | 12D30-N04    | 1              |
| Fagron                   | Prednisolone, micronized | 12D30-no4    | 1              |
| Fagron                   | Prednisolone, micronized | 12D30-N04    | 1              |
| Fagron                   | Prednisolone, micronized | 12K14-N03    | 11             |
| Unisan                   | Prednisolone, micronized | 12K14N-N03   | 1              |
| Gehe                     | Prednisolone, micronized | 13A07-N14    | 2              |
| Caelo                    | Prednisolone, micronized | 13A07-N14    | 2              |
| Fagron                   | Prednisolone, micronized | 12K14-N03    | 1              |
| Phönix                   | Prednisolone, micronized | 13A07N14     | 1              |
| Fargron                  | Prednisolone, micronized | 13E15-N06    | 1              |
| Caelo                    | Prednisolone, micronized | 13e15-n06    | 2              |
| Phönix                   | Prednisolone, micronized | 13E15-N06    | 2              |
| Caelo                    | Prednisolone, micronized | 13E15-N06    | 4              |
| Sanacorp                 | Prednisolone, micronized | 13E15-N06    | 1              |
| AHD, 28.11.13            | Prednisolone, micronized | 13E15-N06    | 1              |
| Fagron                   | Prednisolone, micronized | 13E15-N06    | 1              |
| Gehe                     | Prednisolone, micronized | 13E15-No6    | 1              |
| Phönix                   | Prednisolone, micronized | 15206103     | 1              |
| Caelo                    | Prednisolone, micronized | 20021303     | 1              |
| Caelo                    | Prednisolone, micronized | 411092-1-P   | 1              |
| Caelo                    | Prednisolone, micronized | 2413Q02105   | 1              |

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| Supplier              | Substance                | Batch        | Spectra |
|-----------------------|--------------------------|--------------|---------|
| Caelo                 | Prednisolone, micronized | 4513U2105    | 1       |
| Caelo                 | Prednisolone, micronized | 26131-02105  | 1       |
| Fargon                | Prednisolone, micronized | FP01409P     | 1       |
| Fargon                | Prednisolone, micronized | 4313E-02105  | 1       |
| Fargon                | Prednisolone, micronized | Ch12D30-N04  | 1       |
| Euro OTC              | Prednisolone, micronized | NEPL110103   | 1       |
| Fargon                | Prednisolone, micronized | K04C20121006 | 1       |
| Tianyao Pharma/Phönix | Prednisolone, micronized | NEPL110103   | 1       |
| Fargon                | Prednisolone, micronized | nep1120802   | 1       |
| Fargon                | Prednisolone, micronized | NEPL151202   | 1       |
| Fargon                | Prednisolone, micronized | 11g22-n08    | 1       |

- 68 887 spectra from 414 *Apo-Ident* customers from a total of 23 619 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Prednisolone, micronized* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Prednisolone, micronized* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 799           | 0              | 70 587        |
| <b>Type B</b> | 0              | 471           | 50             | 146 208       |
| <b>Type C</b> | 0              | 725           | 21             | 68 887        |

The substance/substance group *Prednisolone, micronized* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 99.2491 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 90.4031 % (> 89.8273 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 97.1850 % (> 96.7828 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested



reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20773     | 21449               | 17.45                        | 36.36                           |
| 21303     | 21303               | 0.00                         | 29.65                           |
| 21449     | 21449               | 0.00                         | 29.24                           |
| 21604     | 21604               | 0.00                         | 36.84                           |
| 21660     | 21449               | 4.12                         | 29.96                           |
| 21849     | 21849               | 0.00                         | 24.13                           |
| 22435     | 22435               | 0.00                         | 39.36                           |
| 22467     | 22467               | 0.00                         | 21.83                           |
| 22651     | 21303               | 13.03                        | 39.49                           |
| 22709     | 22709               | 0.00                         | 32.36                           |
| 22783     | 22435               | 5.76                         | 36.77                           |
| 22803     | 21604               | 6.07                         | 37.03                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Prednisone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20002-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Prednisone; Prednisonum

### Special notes

When selecting the *Prednisone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Prednisone*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate |
|----------|------------|------------------|-----------|---------|-------------|
| Caelo    | Prednisone | 12232716         | 21408     | 40      | 20120829    |
| Euro OTC | Prednisone | 1401042-02       | 21616     | 40      | 1605276     |
| Euro OTC | Prednisone | 1604051          | 22557     | 40      | 20160523*   |
| Fagron   | Prednisone | 16J19-B02-328642 | 23227     | 40      | 20161221    |
| Caelo    | Prednisone | 12232716         | 21408SI   | 40      | 20120829    |
| Euro OTC | Prednisone | 1604051          | 22557SI   | 40      | 20160523*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Prednisone*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 520 spectra of 15 reference samples from the substance/substance group *Prednisone*.

| Supplier | Substance  | Batch            | Sample ID            | Spectra |
|----------|------------|------------------|----------------------|---------|
| Caelo    | Prednisone | 72123189         | 20002                | 31      |
| Caelo    | Prednisone | 10037803         | 20109                | 40      |
| Caelo    | Prednisone | 12232716         | 21408 <sup>†</sup>   | 20      |
| Caelo    | Prednisone | 12232716         | 21409                | 60      |
| Fagron   | Prednisone | 13C14-B40-289148 | 21573                | 60      |
| Euro OTC | Prednisone | 1401042-02       | 21616 <sup>†</sup>   | 20      |
| Euro OTC | Prednisone | 1702008          | 23179                | 40      |
| Caelo    | Prednisone | 171665           | 23341                | 20      |
| Caelo    | Prednisone | 17166504         | 23578                | 30      |
| Caelo    | Prednisone | 12232716         | 21408SI <sup>†</sup> | 20      |
| Caelo    | Prednisone | 12232716         | 21409SI              | 60      |
| Euro OTC | Prednisone | 1702008          | 23179SI              | 29      |
| Fagron   | Prednisone | 16J19-B02-328642 | 23227SI              | 30      |
| Caelo    | Prednisone | 171665           | 23341SI              | 30      |
| Caelo    | Prednisone | 17166504         | 23578SI              | 30      |

- 146 209 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 39 spectra from 22 *Apo-Ident* customers from 26 batches from the substance/substance group *Prednisone*.

| Supplier    | Substance  | Batch      | Spectra |
|-------------|------------|------------|---------|
| Caelo       | Prednisone | 10037803   | 1       |
| Caelo       | Prednisone | 204312107  | 1       |
| Caelo       | Prednisone | 10037817   | 4       |
| Caelo       | Prednisone | 10037826   | 1       |
| Caelo       | Prednisone | 12177604   | 2       |
| Phönix      | Prednisone | 11D08-N05  | 1       |
| Caelo       | Prednisone | 12232705   | 3       |
| Caelo       | Prednisone | 12232713   | 1       |
| Gehe        | Prednisone | 12232714   | 1       |
| Caelo       | Prednisone | 12232714   | 1       |
| Fagron      | Prednisone | 12E02-N01  | 1       |
| Fagron      | Prednisone | 12E02-N10  | 1       |
| Gehe        | Prednisone | 12L14-M03  | 1       |
| Caelo       | Prednisone | 13262302   | 1       |
| Caelo       | Prednisone | 13262304   | 1       |
| Fagron      | Prednisone | 13C13-N08  | 1       |
| Gehe        | Prednisone | 13C13-N08  | 1       |
| Euro OTC    | Prednisone | 1401042-02 | 1       |
| Euro OTC    | Prednisone | 1501043-03 | 1       |
| Caelo       | Prednisone | 15218602   | 4       |
| Caelo       | Prednisone | 15218606   | 3       |
| Caelo       | Prednisone | 16277206   | 1       |
| Fagron      | Prednisone | 21021401   | 1       |
| Caelo       | Prednisone | 28021401   | 1       |
| Caelo       | Prednisone | 2114Q2107  | 1       |
| Caelo       | Prednisone | 28021403   | 1       |
| Euro/phönix | Prednisone | 140104-02  | 1       |
| Caelo       | Prednisone | 5087       | 1       |

- 69 594 spectra from 414 *Apo-Ident* customers from a total of 23 775 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Prednisone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Prednisone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 240           | 0              | 71 146        |
| Type B | 0              | 520           | 0              | 146 209       |
| Type C | 0              | 38            | 1              | 69 594        |

The substance/substance group *Prednisone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.8462 %) |
| Type C | 100.0000 % (> 99.8813 %) | 97.4359 % (> 89.7436 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21408     | 21616               | 11.11                        | 21.21                           |
| 21616     | 21616               | 0.00                         | 25.88                           |
| 22557     | 22557               | 0.00                         | 33.53                           |
| 23227     | 21616               | 5.05                         | 23.93                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Pregnenolone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20721-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Pregnenolone; Pregnenolonum

### Special notes

When selecting the *Pregnenolone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Pregnenolone*:

| Supplier | Substance    | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------|------------------|-----------|---------|-------------|
| Euro OTC | Pregnenolone | 1204040-01       | 20721     | 40      | 1404311     |
| Euro OTC | Pregnenolone | 1312007-01       | 21679     | 40      | 8985        |
| Fagron   | Pregnenolone | 15B11-B07-310278 | 22355     | 30      | 9338        |
| Euro OTC | Pregnenolone | 1602001          | 22375     | 30      | 20160208*   |
| Euro OTC | Pregnenolone | 1612019          | 22979     | 40      | 20170131*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 180 spectra of 5 reference samples from the substance/substance group *Pregnenolone*. These samples are listed above in the [calibration samples](#) section.
- 71 206 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 170 spectra of 6 reference samples from the substance/substance group *Pregnenolone*.

| Supplier | Substance    | Batch            | Sample ID          | Spectra |
|----------|--------------|------------------|--------------------|---------|
| Euro OTC | Pregnenolone | 2903030-02       | 20612              | 40      |
| Euro OTC | Pregnenolone | 1312007-01       | 21679 <sup>†</sup> | 20      |
| Fagron   | Pregnenolone | 15B11-B07-310278 | 22355 <sup>†</sup> | 15      |
| Euro OTC | Pregnenolone | 1602001          | 22375 <sup>†</sup> | 15      |
| Euro OTC | Pregnenolone | 1606028          | 22706              | 40      |
| Euro OTC | Pregnenolone | 1709017          | 23696              | 40      |

- 146 559 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 14 spectra from 5 *Apo-Ident* customers from 12 batches from the substance/substance group *Pregnenolone*.

| Supplier                   | Substance    | Batch            | Spectra |
|----------------------------|--------------|------------------|---------|
| Euro OTC                   | Pregnenolone | 1402025-01       | 1       |
| Fagron                     | Pregnenolone | 14B18-B04-291917 | 1       |
| NWM CHina                  | Pregnenolone | PR150329         | 1       |
| Haihang Industry           | Pregnenolone | 20140329         | 1       |
| Audor Pharma               | Pregnenolone | APC07-150801(M)P | 1       |
| NWM Shandong Northwest ... | Pregnenolone | PRN151219        | 1       |
| Euro OTC                   | Pregnenolone | 1312007-01       | 1       |
| Audor Pharma               | Pregnenolone | AP10L10-M01P     | 1       |
| Audor Pharma               | Pregnenolone | AP1109007-01P    | 3       |
| KS Pharma                  | Pregnenolone | ZH-111119        | 1       |
| Koisser                    | Pregnenolone | ZH-130802        | 1       |
| Koisser Pharma             | Pregnenolone | ZH-131001        | 1       |

- 69 619 spectra from 414 *Apo-Ident* customers from a total of 23 789 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Pregnenolone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Pregnenolone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 180           | 0              | 71 206        |
| <b>Type B</b> | 0              | 170           | 0              | 146 559       |
| <b>Type C</b> | 0              | 14            | 0              | 69 619        |

The substance/substance group *Pregnenolone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.6667 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.4706 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20721     | 20721               | 0.00                         | 19.59                           |
| 21679     | 21679               | 0.00                         | 17.82                           |
| 22355     | 22355               | 0.00                         | 21.53                           |
| 22375     | 22375               | 0.00                         | 17.86                           |
| 22979     | 22979               | 0.00                         | 18.15                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Prilocaine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21048-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Prilocaine hydrochloride; Prilocaini hydrochloridum; Prilocainum hydrochloricum

### Special notes

When selecting the *Prilocaine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Prilocaine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Prilocaine hydro... | 13I02-N03        | 21048     | 40      | 1403257            |
| Fagron   | Prilocaine hydro... | 14H13-B03-297591 | 21800     | 40      | AR-15-FG-016323-01 |
| Caelo    | Prilocaine hydro... | 15230305         | 21926     | 40      | 20150723           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Prilocaine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 273 spectra of 7 reference samples from the substance/substance group *Prilocaine hydrochloride*.

| Supplier | Substance                | Batch            | Sample ID          | Spectra |
|----------|--------------------------|------------------|--------------------|---------|
| Fagron   | Prilocaine hydrochloride | 13I02-N03        | 21050              | 40      |
| Fagron   | Prilocaine hydrochloride | 14H13-B03-297591 | 21800 <sup>†</sup> | 20      |
| Caelo    | Prilocaine hydrochloride | 15230305         | 21926 <sup>†</sup> | 20      |
| Caelo    | Prilocaine hydrochloride | 15390101         | 23250              | 40      |
| Fagron   | Prilocaine hydrochloride | 14H13-B03-297591 | 21800SI            | 60      |
| Caelo    | Prilocaine hydrochloride | 15230305         | 21926SI            | 60      |
| Caelo    | Prilocaine hydrochloride | 15390101         | 23250SI            | 33      |

- 146 456 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 2 spectra from 2 *Apo-Ident* customers from 2 batches from the substance/substance group *Prilocaine hydrochloride*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier        | Substance                | Batch      | Spectra |
|-----------------|--------------------------|------------|---------|
| Fagron          | Prilocaine hydrochloride | 13I032-N03 | 1       |
| GEHE 02.05.2013 | Prilocaine hydrochloride |            | 1       |

- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Prilocaine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Prilocaine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 247           | 26             | 146 456       |
| <b>Type C</b> | 0              | 2             | 0              | 69 631        |

The substance/substance group *Prilocaine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 90.4762 % (> 89.3773 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21048     | 21048               | 0.00                         | 46.45                           |
| 21800     | 21800               | 0.00                         | 46.76                           |
| 21926     | 21800               | 8.10                         | 49.06                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Procaine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20042-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Procaine hydrochloride; Procaini hydrochloridum; Procainum hydrochloricum

### Special notes

When selecting the *Procaine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Procaine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Caelo    | Procaine hydroch... | 13109906         | 21785     | 40      | AR-15-FG-008935-01 |
| Caelo    | Procaine hydroch... | 15006906         | 22247     | 40      | 20150209           |
| Fagron   | Procaine hydroch... | 13F12-B40-301798 | 22260     | 40      | 20141210           |
| Euro OTC | Procaine hydroch... | 1601014          | 22306     | 40      | 20160203*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Procaine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 270 spectra of 9 reference samples from the substance/substance group *Procaine hydrochloride*.

| Supplier | Substance              | Batch            | Sample ID          | Spectra |
|----------|------------------------|------------------|--------------------|---------|
| Fagron   | Procaine hydrochloride | 8L11-N12         | 20042              | 30      |
| Euro OTC | Procaine hydrochloride | 1003001-01       | 20542              | 40      |
| Caelo    | Procaine hydrochloride | 13109906         | 21785 <sup>†</sup> | 20      |
| Caelo    | Procaine hydrochloride | 15006906         | 22247 <sup>†</sup> | 20      |
| Fagron   | Procaine hydrochloride | 13F12-B40-301798 | 22260 <sup>†</sup> | 20      |
| Euro OTC | Procaine hydrochloride | 1601014          | 22306 <sup>†</sup> | 20      |
| Caelo    | Procaine hydrochloride | 161378           | 22624              | 40      |
| Fagron   | Procaine hydrochloride | 15J27-B10-322937 | 23379              | 40      |
| Caelo    | Procaine hydrochloride | 171675           | 23634              | 40      |

- 146 459 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 88 spectra from 52 *Apo-Ident* customers from 51 batches from the substance/substance group *Procaine hydrochloride*.

| Supplier                   | Substance              | Batch            | Spectra |
|----------------------------|------------------------|------------------|---------|
| Euro OTC                   | Procaine hydrochloride | 1104012-04       | 5       |
| Caelo                      | Procaine hydrochloride | 7011506          | 1       |
| Euro OTC                   | Procaine hydrochloride | 1104012-05       | 5       |
| Fagron                     | Procaine hydrochloride | 13/30-N06        | 1       |
| Alliance Health 09.09.2... | Procaine hydrochloride | 1104012-05       | 1       |
| Fagron                     | Procaine hydrochloride | 13I09-N08        | 1       |
| Caelo                      | Procaine hydrochloride | 13109905         | 1       |
| Caelo                      | Procaine hydrochloride | 13109906         | 2       |
| Caelo                      | Procaine hydrochloride | 1310880          | 1       |
| Caelo                      | Procaine hydrochloride | 13109916         | 1       |
| Euro OTC                   | Procaine hydrochloride | 1405027-01       | 5       |
| Caelo                      | Procaine hydrochloride | 13F12-B40-302510 | 1       |
| Fagron                     | Procaine hydrochloride | 13F12-B40        | 1       |
| Euro OTC                   | Procaine hydrochloride | 1405027-02       | 1       |
| Caelo                      | Procaine hydrochloride | 14164408         | 1       |
| Caelo                      | Procaine hydrochloride | 14164409         | 3       |
| Caesar & Loretz GmbH       | Procaine hydrochloride | 14164413         | 1       |
| Caelo                      | Procaine hydrochloride | 14164413         | 1       |
| Caelo                      | Procaine hydrochloride | 15006906         | 2       |
| Caelo                      | Procaine hydrochloride | 15006902         | 1       |
| Caelo                      | Procaine hydrochloride | 15006912         | 1       |
| Caesar & Loretz GmbH       | Procaine hydrochloride | 15006907         | 1       |
| Caelo                      | Procaine hydrochloride | 15006913         | 1       |
| Euro OTC                   | Procaine hydrochloride | 1601014-01       | 5       |
| siehe WE-Prüfprotokoll     | Procaine hydrochloride | 39/12            | 1       |
| Gatt-Koller / Phoenix      | Procaine hydrochloride | 4428/10122714    | 2       |
| Euro OTC                   | Procaine hydrochloride | 5127             | 1       |
| Caelo                      | Procaine hydrochloride | 60998127         | 2       |
| Kehr                       | Procaine hydrochloride | 10159721         | 1       |
| Caelo                      | Procaine hydrochloride | 10159721         | 1       |
| Caelo                      | Procaine hydrochloride | 10159723         | 1       |
| Caelo                      | Procaine hydrochloride | 10159729         | 1       |
| Phönix Gotha               | Procaine hydrochloride | 190311           | 1       |
| Euro OTC                   | Procaine hydrochloride | 1003001-01       | 1       |
| Gehe                       | Procaine hydrochloride | 10159730         | 1       |
| Fagron                     | Procaine hydrochloride | 10H11-N25        | 1       |
| Euro OTC                   | Procaine hydrochloride | 1104012-03       | 4       |
| Gehe                       | Procaine hydrochloride | 1104012-03       | 1       |
| Euro OTC                   | Procaine hydrochloride | 1104012-01       | 1       |
| Phönix 08.01.2014          | Procaine hydrochloride | 1104012-03       | 1       |
| Caelo                      | Procaine hydrochloride | 11370203         | 1       |
| Koisser                    | Procaine hydrochloride | 11370218         | 1       |
| Caelo                      | Procaine hydrochloride | 11370206         | 1       |
| Caelo                      | Procaine hydrochloride | 11370215         | 1       |
| Caelo                      | Procaine hydrochloride | 11370204         | 1       |
| Caelo                      | Procaine hydrochloride | 12177801         | 3       |
| Caelo                      | Procaine hydrochloride | 11370219         | 1       |
| Caelo                      | Procaine hydrochloride | 11370216         | 2       |
| Herstellung                | Procaine hydrochloride | 12177801         | 1       |
| Caelo                      | Procaine hydrochloride | 13109908         | 2       |
| China Medica               | Procaine hydrochloride | 13109911         | 1       |
| Caelo                      | Procaine hydrochloride | 13109915         | 1       |

*continued on the next page*

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| Supplier | Substance              | Batch     | Spectra |
|----------|------------------------|-----------|---------|
| Fagron   | Procaine hydrochloride | 12I10-N07 | 2       |
| Caelo    | Procaine hydrochloride | 131099903 | 1       |
| Caelo    | Procaine hydrochloride | 13I09-N08 | 1       |
| Anzag    | Procaine hydrochloride | 60998058  | 1       |
| Euro OTC | Procaine hydrochloride | 200644    | 1       |
| Fagron   | Procaine hydrochloride | 1651212   | 1       |

- 69 545 spectra from 414 *Apo-Ident* customers from a total of 23 750 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Procaine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Procaine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 270           | 0              | 146 459       |
| <b>Type C</b> | 0              | 85            | 3              | 69 545        |

The substance/substance group *Procaine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.7778 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 96.5909 % (> 93.1818 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21785     | 21785               | 0.00                         | 37.46                           |
| 22247     | 21785               | 6.32                         | 39.34                           |
| 22260     | 21785               | 5.44                         | 39.29                           |
| 22306     | 22306               | 0.00                         | 36.76                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Progesterone, micronized**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20024-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Progesterone, micronized; Progesteronum micronisatum

### Special notes

When selecting the *Progesterone, micronized* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Progesterone, micronized*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Euro OTC | Progesterone, mi... | 1111053-01 | 20718     | 30      | 20120119    |
| Euro OTC | Progesterone, mi... | 1506033    | 21868     | 20      | 0000010482  |
| Euro OTC | Progesterone, mi... | 1506034    | 21870     | 40      | 0000010483  |
| Euro OTC | Progesterone, mi... | 1509008    | 21907     | 40      | 20150914*   |
| Euro OTC | Progesterone, mi... | 1511008    | 22226     | 40      | 20151119*   |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Progesterone, mi... | 1601009          | 22301     | 30      | 20160128*   |
| Euro OTC | Progesterone, mi... | 1601001          | 22303     | 30      | 20160128*   |
| Euro OTC | Progesterone, mi... | 1603004          | 22525     | 40      | 20160406*   |
| Fagron   | Progesterone, mi... | 16A20-B02-319103 | 22830     | 40      | 20160209    |
| Caelo    | Progesterone, mi... | 15319601         | 22831     | 40      | 20151014    |
| Euro OTC | Progesterone, mi... | 1506033          | 21868SI   | 20      | 0000010482  |
| Euro OTC | Progesterone, mi... | 1601009          | 22301SI   | 30      | 20160128*   |
| Fagron   | Progesterone, mi... | 16A20-B02-319103 | 22830SI   | 40      | 20160209    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 440 spectra of 13 reference samples from the substance/substance group *Progesterone, micronized*. These samples are listed above in the [calibration samples](#) section.
- 70 946 spectra from a total of 1542 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 1359 spectra of 41 reference samples from the substance/substance group *Progesterone, micronized*.

| Supplier | Substance                | Batch     | Sample ID          | Spectra |
|----------|--------------------------|-----------|--------------------|---------|
| Caelo    | Progesterone, micronized | 71498458  | 20024              | 60      |
| Fagron   | Progesterone, micronized | 12A19-N04 | 20546              | 40      |
| Caelo    | Progesterone, micronized | 80277304  | 21018              | 30      |
| Euro OTC | Progesterone, micronized | 1506033   | 21868 <sup>†</sup> | 40      |
| Euro OTC | Progesterone, micronized | 1506034   | 21870 <sup>†</sup> | 20      |
| Euro OTC | Progesterone, micronized | 1509008   | 21907 <sup>†</sup> | 20      |
| Euro OTC | Progesterone, micronized | 1511008   | 22226 <sup>†</sup> | 20      |
| Euro OTC | Progesterone, micronized | 1601009   | 22301 <sup>†</sup> | 15      |
| Euro OTC | Progesterone, micronized | 1601001   | 22303 <sup>†</sup> | 15      |
| Euro OTC | Progesterone, micronized | 1603012   | 22529              | 40      |
| Euro OTC | Progesterone, micronized | 1605013   | 22556              | 40      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

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| Supplier | Substance                | Batch    | Sample ID            | Spectra |
|----------|--------------------------|----------|----------------------|---------|
| Euro OTC | Progesterone, micronized | 1606033  | 22704                | 40      |
| Euro OTC | Progesterone, micronized | 1605032  | 22705                | 40      |
| Euro OTC | Progesterone, micronized | 1609016  | 22788                | 40      |
| Euro OTC | Progesterone, micronized | 1609001  | 22819                | 40      |
| Euro OTC | Progesterone, micronized | 1701038  | 23138                | 40      |
| Euro OTC | Progesterone, micronized | 1702026  | 23148                | 40      |
| Caelo    | Progesterone, micronized | 17060903 | 23249                | 40      |
| Caelo    | Progesterone, micronized | 170609   | 23329                | 40      |
| Euro OTC | Progesterone, micronized | 1707012  | 23536                | 40      |
| Euro OTC | Progesterone, micronized | 1705028  | 23541                | 40      |
| Euro OTC | Progesterone, micronized | 1506033  | 21868SI <sup>†</sup> | 30      |
| Euro OTC | Progesterone, micronized | 1506034  | 21870SI              | 59      |
| Euro OTC | Progesterone, micronized | 1509008  | 21907SI              | 53      |
| Euro OTC | Progesterone, micronized | 1511008  | 22226SI              | 27      |
| Euro OTC | Progesterone, micronized | 1601009  | 22301SI <sup>†</sup> | 15      |
| Euro OTC | Progesterone, micronized | 1601001  | 22303SI              | 44      |
| Euro OTC | Progesterone, micronized | 1603004  | 22525SI              | 31      |
| Euro OTC | Progesterone, micronized | 1603012  | 22529SI              | 29      |
| Euro OTC | Progesterone, micronized | 1605013  | 22556SI              | 30      |
| Euro OTC | Progesterone, micronized | 1606033  | 22704SI              | 30      |
| Euro OTC | Progesterone, micronized | 1605032  | 22705SI              | 38      |
| Euro OTC | Progesterone, micronized | 1609016  | 22788SI              | 30      |
| Euro OTC | Progesterone, micronized | 1609001  | 22819SI              | 30      |
| Caelo    | Progesterone, micronized | 15319601 | 22831SI              | 40      |
| Euro OTC | Progesterone, micronized | 1701038  | 23138SI              | 20      |
| Euro OTC | Progesterone, micronized | 1702026  | 23148SI              | 20      |
| Caelo    | Progesterone, micronized | 17060903 | 23249SI              | 20      |
| Caelo    | Progesterone, micronized | 170609   | 23329SI              | 20      |
| Euro OTC | Progesterone, micronized | 1707012  | 23536SI              | 28      |
| Euro OTC | Progesterone, micronized | 1705028  | 23541SI              | 25      |

- 145 370 spectra from a total of 3171 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 437 spectra from 139 *Apo-Ident* customers from 180 batches from the substance/substance group *Progesterone, micronized*.

| Supplier      | Substance                | Batch    | Spectra |
|---------------|--------------------------|----------|---------|
| Caelo         | Progesterone, micronized | 12195924 | 3       |
| Caelo         | Progesterone, micronized | 12195828 | 1       |
| Caesar/Noweda | Progesterone, micronized | 12195912 | 1       |
| Euro OTC      | Progesterone, micronized | 12195924 | 1       |
| Caelo         | Progesterone, micronized | 7101401  | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier                 | Substance                | Batch             | Spectra |
|--------------------------|--------------------------|-------------------|---------|
| Caelo                    | Progesterone, micronized | 12195926          | 20      |
| Caelo                    | Progesterone, micronized | 12195928          | 10      |
| keine Angabe             | Progesterone, micronized | 1304040-01        | 1       |
| Euro OTC                 | Progesterone, micronized | 1304040-02        | 3       |
| Changzhou Jiaerke Pharma | Progesterone, micronized | 1308015-01        | 1       |
| Euro OTC                 | Progesterone, micronized | 1308015-01        | 3       |
| Vdl 28.04.14;Preis 39,95 | Progesterone, micronized |                   | 1       |
| Caelo                    | Progesterone, micronized | 13155902          | 10      |
| Caelo                    | Progesterone, micronized | 13155920          | 1       |
| Phönix                   | Progesterone, micronized | 13155920          | 1       |
| Caesar u Loretz          | Progesterone, micronized | 13155920          | 1       |
| Caelo                    | Progesterone, micronized | 13155921          | 2       |
| VDL;07.11.14;39,95 euro  | Progesterone, micronized | 13155921          | 1       |
| Caelo                    | Progesterone, micronized | 13155927          | 3       |
| Caelo                    | Progesterone, micronized | 13155928          | 3       |
| Caelo                    | Progesterone, micronized | 13155929          | 3       |
| Phoenix 28.03.2014       | Progesterone, micronized | 13G11-N02         | 1       |
| PHOENIX am 18.03.2014    | Progesterone, micronized | 13A02-N01         | 1       |
| Caelo                    | Progesterone, micronized | 13G11-N02         | 1       |
| Fagron                   | Progesterone, micronized | 13G11-N02         | 11      |
| Fagron                   | Progesterone, micronized | 13H01-N03         | 7       |
| Phoenix 09.12.14         | Progesterone, micronized | 13H01-N03         | 1       |
| Caelo                    | Progesterone, micronized | 13HI01-N03        | 1       |
| Fagron                   | Progesterone, micronized | 13K28-B30-288261  | 2       |
| Fagron                   | Progesterone, micronized | 13K28-B30-288263  | 1       |
| Fagron                   | Progesterone, micronized | 13k28-b30-288262  | 1       |
| Fagron                   | Progesterone, micronized | 13K28-B30-288262  | 2       |
| Euro OTC                 | Progesterone, micronized | 1401002-01        | 5       |
| Caelo                    | Progesterone, micronized | 140100201         | 1       |
| EuRho                    | Progesterone, micronized | 1401002-01        | 2       |
| Dorfmeister              | Progesterone, micronized | 140301-01         | 1       |
| Euro OTC                 | Progesterone, micronized | 1403019-01        | 3       |
| Euro OTC                 | Progesterone, micronized | 140602201         | 1       |
| Euro OTC                 | Progesterone, micronized | 1406022-01        | 1       |
| Europh-Jenne             | Progesterone, micronized | 1406022-01        | 1       |
| Euro OTC                 | Progesterone, micronized | 1406022-02        | 2       |
| Euro OTC                 | Progesterone, micronized | 1409010-01        | 1       |
| Euro OTC                 | Progesterone, micronized | 1409029-01        | 3       |
| Euro OTC                 | Progesterone, micronized | 1406910-01        | 1       |
| Euro OTC                 | Progesterone, micronized | 140602202         | 1       |
| Euro OTC                 | Progesterone, micronized | 140901001         | 1       |
| Euro OTC                 | Progesterone, micronized | 1409019-01        | 1       |
| Euro OTC                 | Progesterone, micronized | 140910-01         | 1       |
| Euro OTC                 | Progesterone, micronized | 1411043-01        | 4       |
| Caelo                    | Progesterone, micronized | 14253906          | 4       |
|                          | Progesterone, micronized | 14253906          | 1       |
| Caelo                    | Progesterone, micronized | 14253911          | 3       |
| Fagron                   | Progesterone, micronized | 14C10-B01         | 1       |
| Caelo                    | Progesterone, micronized | 14253915          | 2       |
| Fagron                   | Progesterone, micronized | 14D22-B04         | 2       |
| Caelo                    | Progesterone, micronized | 14253929          | 2       |
| Fagron                   | Progesterone, micronized | 14D22-B04-293477  | 2       |
| Fagron                   | Progesterone, micronized | 14G01-B06         | 1       |
| Fagron                   | Progesterone, micronized | 14D22-B293479     | 1       |
| Fagron                   | Progesterone, micronized | 14H13-B05-300216  | 2       |
| Fagron                   | Progesterone, micronized | 14K11-B04         | 3       |
| Caelo                    | Progesterone, micronized | 14H13-B05-3002016 | 1       |
| Fagron                   | Progesterone, micronized | 14K11-B04300921   | 1       |
| Fagron                   | Progesterone, micronized | 14k11-b04         | 1       |
| Fagron                   | Progesterone, micronized | 14K11-B04-300920  | 5       |

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| Supplier                   | Substance                | Batch             | Spectra |
|----------------------------|--------------------------|-------------------|---------|
| Caelo                      | Progesterone, micronized | 14K11-B04-300920  | 1       |
| Fagron                     | Progesterone, micronized | 14K11-B04-300922  | 1       |
| Fagron                     | Progesterone, micronized | 14L15-B05-302292  | 1       |
| Fagron                     | Progesterone, micronized | 14022-B04-293476  | 1       |
| Fagron                     | Progesterone, micronized | 14K11-B04-300923  | 1       |
| Euro OTC                   | Progesterone, micronized | 1502030-01        | 2       |
| Euro OTC                   | Progesterone, micronized | 1503012-01        | 3       |
| Euro OTC                   | Progesterone, micronized | 1506033-01        | 5       |
| Euro OTC                   | Progesterone, micronized | 1509008-01        | 5       |
| Euro OTC                   | Progesterone, micronized | 150900801         | 1       |
| Euro OTC                   | Progesterone, micronized | 1509008-02        | 1       |
| Caelo                      | Progesterone, micronized | 15124919          | 1       |
| Caelo                      | Progesterone, micronized | 15124902          | 1       |
| Caelo                      | Progesterone, micronized | 15124910          | 1       |
| sanacorp                   | Progesterone, micronized | 15124902          | 1       |
| Caelo                      | Progesterone, micronized | 1511-B05-313598   | 1       |
| Caesar u Loretz            | Progesterone, micronized | 15124919          | 1       |
| Caelo                      | Progesterone, micronized | 15319601          | 1       |
| Caelo                      | Progesterone, micronized | 15319602          | 2       |
| Caelo                      | Progesterone, micronized | 15319607          | 2       |
| Phönix                     | Progesterone, micronized | 15319604          | 1       |
| Sanacorp, 16.08.2016, 4... | Progesterone, micronized | 15319607          | 1       |
| Caelo                      | Progesterone, micronized | 15319618          | 3       |
| Caelo                      | Progesterone, micronized | 15319619          | 1       |
| Fagron                     | Progesterone, micronized | 15B12-B04-304838  | 1       |
| Fagron                     | Progesterone, micronized | 15C31-B06         | 2       |
| Fagron                     | Progesterone, micronized | 15B12-B04-304838  | 1       |
| Fagron                     | Progesterone, micronized | 15C31-B06-308439  | 2       |
| Fagron                     | Progesterone, micronized | 15C31-B06-308796  | 4       |
| Ebert u. Jacobi 16.0...    | Progesterone, micronized | 15C31-B06-312963  | 1       |
| Fagron                     | Progesterone, micronized | 15C31-B06-309790  | 2       |
| Fagron                     | Progesterone, micronized | 15C31-B06-316105  | 3       |
| Fagron                     | Progesterone, micronized | 15C31-B06-313599  | 1       |
| Caelo                      | Progesterone, micronized | 15I11-B05-314184  | 2       |
| Fagron                     | Progesterone, micronized | 15I11-B05-314184  | 1       |
| Fagron                     | Progesterone, micronized | 15I11-B05-314842  | 1       |
| Fagron                     | Progesterone, micronized | 15I11-B05-315224  | 1       |
| Euro OTC                   | Progesterone, micronized | 1601009-01        | 4       |
| Caelo                      | Progesterone, micronized | 160100902         | 1       |
| Euro OTC                   | Progesterone, micronized | 1605013-01        | 1       |
| Phönix                     | Progesterone, micronized | 1605013-01        | 1       |
| Euro OTC                   | Progesterone, micronized | 1601009-02        | 2       |
| Euro OTC                   | Progesterone, micronized | 1605013-02        | 1       |
| Caelo                      | Progesterone, micronized | 16103602          | 3       |
| Fagron                     | Progesterone, micronized | 16A20-B02-318667  | 3       |
| Caelo                      | Progesterone, micronized | 16A20-B02-319103  | 1       |
| Fagron                     | Progesterone, micronized | 16A20-B02-321373  | 1       |
| Fagron                     | Progesterone, micronized | 16A20-B02-321374  | 2       |
| Fagron                     | Progesterone, micronized | 16g115-b04-325136 | 1       |
| Fagron                     | Progesterone, micronized | 16G15-B04-325136  | 1       |
| Fagron                     | Progesterone, micronized | 16G15-B04-32579   | 1       |
| Caelo                      | Progesterone, micronized | 16L29-B03-330995  | 1       |
| Fagron                     | Progesterone, micronized | 16L29-B03         | 1       |
| Ebert-Jacobi               | Progesterone, micronized | 16J05-B04-328263  | 1       |
| Caelo                      | Progesterone, micronized | 19051502          | 1       |
| Fagron                     | Progesterone, micronized | 2006500007        | 1       |
| Fagron                     | Progesterone, micronized | 5013I-03235       | 1       |
| Euro OTC                   | Progesterone, micronized | 5102              | 1       |
| Euro OTC                   | Progesterone, micronized | 5104              | 1       |
| Euro OTC                   | Progesterone, micronized | 7406022-01        | 1       |

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| Supplier                  | Substance                | Batch          | Spectra |
|---------------------------|--------------------------|----------------|---------|
| Audor Pharma              | Progesterone, micronized | APC01-120613P  | 1       |
| Audor Pharma              | Progesterone, micronized | APC01-150708P  | 3       |
| Audor Pharma              | Progesterone, micronized | APC01-141212P  | 1       |
| Audor Pharma              | Progesterone, micronized | APC01-150311P  | 1       |
| Anzag 07.04.2016          | Progesterone, micronized | APC01-150708P  | 1       |
| Audor Pharma              | Progesterone, micronized | APC01-151114P  | 3       |
| Audor Pharma              | Progesterone, micronized | APC01-160201P  | 1       |
| Fagron                    | Progesterone, micronized | HTT140302      | 1       |
| Caelo                     | Progesterone, micronized | HTT140302      | 1       |
| Audor Pharma              | Progesterone, micronized | APC01-160201   | 1       |
| Euro/ Sanacorp            | Progesterone, micronized | C01-131116 (M) | 1       |
| Gehe                      | Progesterone, micronized | 1111053-01     | 4       |
| Euro OTC                  | Progesterone, micronized | 11110523-01    | 1       |
| Caelo                     | Progesterone, micronized | 9195408        | 1       |
| Euro OTC                  | Progesterone, micronized | 1111053-01     | 10      |
| Fagron                    | Progesterone, micronized | 12A19-N04      | 3       |
| Caelo                     | Progesterone, micronized | 12A19-N04      | 2       |
| A.H. 03.06.13 ek: 6,50EUR | Progesterone, micronized | 1304014-01     | 1       |
| Fagron                    | Progesterone, micronized | 1910213235     | 1       |
| Fagron                    | Progesterone, micronized | 1-111218       | 1       |
| Klenk                     | Progesterone, micronized | C01-120322     | 1       |
| FARGON                    | Progesterone, micronized | 10a21-n18      | 1       |
| Euro OTC                  | Progesterone, micronized |                | 1       |
| Caelo                     | Progesterone, micronized | 9195429        | 1       |
| Caelo                     | Progesterone, micronized | 11177207       | 2       |
| Caelo                     | Progesterone, micronized | 11177219       | 3       |
| Caelo                     | Progesterone, micronized | 11177221       | 3       |
| Euro OTC                  | Progesterone, micronized | 1206024-01     | 2       |
| Alliance Healthcare       | Progesterone, micronized | 1206024-02     | 1       |
| Euro OTC                  | Progesterone, micronized | 1211004-01     | 6       |
| Caelo                     | Progesterone, micronized | 12195902       | 1       |
| Caelo                     | Progesterone, micronized | 12195905       | 2       |
| Euro OTC                  | Progesterone, micronized | 12111004-01    | 1       |
| Caelo                     | Progesterone, micronized | 12195906       | 4       |
| Caelo                     | Progesterone, micronized | 12195907       | 6       |
| ANZAG                     | Progesterone, micronized | 12195907       | 2       |
| Caelo                     | Progesterone, micronized | 12195912       | 3       |
| Caelo                     | Progesterone, micronized | 12195913       | 3       |
| Caelo                     | Progesterone, micronized | 12195914       | 2       |
| Caelo                     | Progesterone, micronized | 12195920       | 10      |
| Sanacorp                  | Progesterone, micronized | 12195914       | 1       |
| Phoenix                   | Progesterone, micronized | 12195928       | 3       |
| Sanacorp                  | Progesterone, micronized | 12195928       | 1       |
| Fagron                    | Progesterone, micronized | 12D05-N06      | 5       |
| Fagron                    | Progesterone, micronized | 12a19-n04      | 1       |
| Fagron                    | Progesterone, micronized | 12G05-N17      | 10      |
| Fagron                    | Progesterone, micronized | 12K05-N01      | 2       |
| Fagron                    | Progesterone, micronized | 12K05-N07      | 2       |
| Fagron                    | Progesterone, micronized | 12k05-n07      | 1       |
| FARGON                    | Progesterone, micronized | 13/11-n11      | 1       |
| Fagron                    | Progesterone, micronized | 13/11-N11      | 1       |
| Fagron                    | Progesterone, micronized | 1311-N11       | 1       |
| Euro OTC                  | Progesterone, micronized | 1304040-01     | 4       |
| EuRho                     | Progesterone, micronized | 1304040-02     | 1       |
| Euro OTC                  | Progesterone, micronized | 130404001      | 1       |
| Caelo                     | Progesterone, micronized | 130404002      | 2       |
| Caelo                     | Progesterone, micronized | 1304040-01     | 1       |
| Euro OTC                  | Progesterone, micronized | 1304040-2      | 1       |
| Apotärze                  | Progesterone, micronized | 1304040-02     | 1       |
| China Medica              | Progesterone, micronized | 1308015-01     | 1       |

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| Supplier                | Substance                | Batch            | Spectra |
|-------------------------|--------------------------|------------------|---------|
| Fagron                  | Progesterone, micronized | 13A02N01         | 1       |
| Synopharm am 10.09.2012 | Progesterone, micronized | 13A02-N01        | 1       |
| Fagron                  | Progesterone, micronized | 13A02-N01        | 4       |
| Caelo                   | Progesterone, micronized | 13A02-N01        | 3       |
| Sanacorp                | Progesterone, micronized | 13155902         | 1       |
| Fagron                  | Progesterone, micronized | 13A02-N02        | 1       |
| Fagron                  | Progesterone, micronized | 13b08-n01        | 1       |
| Fagron                  | Progesterone, micronized | 13I11-N11        | 2       |
| Fagron                  | Progesterone, micronized | 13K28-B30-28826  | 1       |
| Fagron                  | Progesterone, micronized | 13K-B30-288261   | 1       |
| Fagron                  | Progesterone, micronized | 1401002-01       | 2       |
| Euro OTC                | Progesterone, micronized | 1409029-1        | 1       |
| Fagron                  | Progesterone, micronized | 14C10-B01-293478 | 1       |
| Fagron                  | Progesterone, micronized | 14C10B0129347    | 1       |
| Caelo                   | Progesterone, micronized | 27121303         | 1       |
| fargon                  | Progesterone, micronized | 8577420          | 1       |
| Audor Pharma            | Progesterone, micronized | APC01-120708P    | 3       |
| Euro OTC                | Progesterone, micronized | 200650           | 1       |
| Euro OTC                | Progesterone, micronized | c01-111218       | 1       |
| Fagron                  | Progesterone, micronized | C01-120322       | 1       |
| Fagron                  | Progesterone, micronized | C01-120613       | 1       |
| Caelo                   | Progesterone, micronized | C01-120613       | 1       |
| Audor Pharma            | Progesterone, micronized | C01-120708P      | 1       |
| Euro OTC                | Progesterone, micronized | c01-130301       | 1       |
| Fagron                  | Progesterone, micronized | C01-130301       | 1       |
| Euro OTC                | Progesterone, micronized | C01-130301 (M)   | 2       |
| Sanacorp                | Progesterone, micronized | C01-130504       | 1       |
| Euro OTC                | Progesterone, micronized | C01-130301M      | 1       |
| Euro OTC                | Progesterone, micronized | co1-111218 (M)   | 1       |
| Fagron                  | Progesterone, micronized | HTT140207        | 1       |
| Gehe                    | Progesterone, micronized | 9195429          | 1       |
| FARGON                  | Progesterone, micronized |                  | 1       |
| Fagron                  | Progesterone, micronized | 12D05N06         | 1       |
| Caelo                   | Progesterone, micronized | 9195419          | 1       |
| Dorfmeister             | Progesterone, micronized | 1304040-02       | 1       |
| Sanacorp                | Progesterone, micronized | 13A02-N01        | 1       |
| AHD                     | Progesterone, micronized | 13I11-N11        | 1       |

- 69 196 spectra from 414 *Apo-Ident* customers from a total of 23 623 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Progesterone, micronized* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Progesterone, micronized* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 440           | 0              | 70 946        |
| <b>Type B</b> | 0              | 1359          | 0              | 145 370       |
| <b>Type C</b> | 0              | 433           | 4              | 69 196        |

The substance/substance group *Progesterone, micronized* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.6364 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 99.5585 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 99.0847 % (> 98.3982 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 20718            | 21907                      | 4.63                                | 17.89                                  |
| 21868            | 21868                      | 0.00                                | 14.18                                  |
| 21870            | 21870                      | 0.00                                | 18.92                                  |
| 21907            | 21907                      | 0.00                                | 17.91                                  |
| 22226            | 22226                      | 0.00                                | 19.92                                  |
| 22301            | 22301                      | 0.00                                | 17.34                                  |
| 22303            | 22303                      | 0.00                                | 16.12                                  |
| 22525            | 22525                      | 0.00                                | 28.11                                  |
| 22830            | 22301                      | 2.84                                | 22.10                                  |
| 22831            | 21907                      | 2.90                                | 20.76                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Promethazine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20208-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Promethazine hydrochloride; Promethazini hydrochloridum; Promethazinum hydrochloricum

### Special notes

When selecting the *Promethazine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Promethazine hydrochloride*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Promethazine hyd... | 13119214 | 21690     | 40      | 20130506    |
| Caelo    | Promethazine hyd... | 161466   | 22628     | 40      | 20160621*   |
| Caelo    | Promethazine hyd... | 17058601 | 23248     | 40      | 20170310    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Promethazine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *Promethazine hydrochloride*.

| Supplier | Substance                  | Batch    | Sample ID          | Spectra |
|----------|----------------------------|----------|--------------------|---------|
| Caelo    | Promethazine hydrochloride | 10334401 | 20208              | 40      |
| Caelo    | Promethazine hydrochloride | 13119214 | 21690 <sup>†</sup> | 20      |
| Caelo    | Promethazine hydrochloride | 170586   | 23324              | 40      |

- 146 629 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 4 spectra from 3 *Apo-Ident* customers from 4 batches from the substance/substance group *Promethazine hydrochloride*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance                  | Batch    | Spectra |
|----------|----------------------------|----------|---------|
| Caelo    | Promethazine hydrochloride | 14336505 | 1       |
| Caelo    | Promethazine hydrochloride | 13119211 | 1       |
| Caelo    | Promethazine hydrochloride | 17058601 | 1       |
| Caelo    | Promethazine hydrochloride | 11352305 | 1       |

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

### Validation results

The validation runs checked whether the substance/substance group *Promethazine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Promethazine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 100           | 0              | 146 629       |
| <b>Type C</b> | 0              | 4             | 0              | 69 629        |

The substance/substance group *Promethazine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21690     | 22628               | 7.32                         | 59.79                           |
| 22628     | 22628               | 0.00                         | 65.03                           |
| 23248     | 22628               | 5.71                         | 60.53                           |



Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Propranolol hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20954-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Propranolol hydrochloride; Propranololi hydrochloridum; Propranololum hydrochloricum

### Special notes

When selecting the *Propranolol hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Propranolol hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | Propranolol hydr... | 13I13-N04        | 20954     | 40      | 1402307     |
| Caelo    | Propranolol hydr... | 12370712         | 21396     | 40      | 20130116    |
| Caelo    | Propranolol hydr... | 12370712         | 21410     | 40      | 20130116    |
| Fagron   | Propranolol hydr... | 15F16-B02-312979 | 22591     | 40      | 20150630    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Propranolol hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 161 spectra of 5 reference samples from the substance/substance group *Propranolol hydrochloride*.

| Supplier | Substance                 | Batch     | Sample ID          | Spectra |
|----------|---------------------------|-----------|--------------------|---------|
| Fagron   | Propranolol hydrochloride | 10C15-N15 | 20253              | 41      |
| Caelo    | Propranolol hydrochloride | 12370712  | 21396 <sup>†</sup> | 20      |
| Caelo    | Propranolol hydrochloride | 12370712  | 21410 <sup>†</sup> | 20      |
| Caelo    | Propranolol hydrochloride | 15283302  | 22590              | 40      |
| Caelo    | Propranolol hydrochloride | 171722    | 23650              | 40      |

- 146 568 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 200 spectra from 114 *Apo-Ident* customers from 68 batches from the substance/substance group *Propranolol hydrochloride*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                   | Substance                 | Batch            | Spectra |
|----------------------------|---------------------------|------------------|---------|
| Fagron                     | Propranolol hydrochloride | 12K06-N07        | 9       |
| Caelo                      | Propranolol hydrochloride | 12370709         | 2       |
| Fagron                     | Propranolol hydrochloride | 11D01-N11        | 1       |
| Fagron                     | Propranolol hydrochloride | 4071401          | 1       |
| Caelo                      | Propranolol hydrochloride | 12370710         | 2       |
| Sanacorp                   | Propranolol hydrochloride | 12370712         | 1       |
| Caelo                      | Propranolol hydrochloride | 12370712         | 1       |
| Caelo                      | Propranolol hydrochloride | 13/13-N04        | 4       |
| Caelo                      | Propranolol hydrochloride | 13379804         | 1       |
| Fagron                     | Propranolol hydrochloride | 1313-N04         | 2       |
| Fagron                     | Propranolol hydrochloride | 13I13-N04        | 8       |
| Euro OTC                   | Propranolol hydrochloride | 13379806         | 1       |
| Caelo                      | Propranolol hydrochloride | 13379806         | 1       |
| Caelo                      | Propranolol hydrochloride | 13379807         | 3       |
| Caesar u Loretz            | Propranolol hydrochloride | 13379807         | 1       |
| Caelo                      | Propranolol hydrochloride | 13379809         | 4       |
| Fagron                     | Propranolol hydrochloride | 13E13-B40-289355 | 1       |
| Fagron                     | Propranolol hydrochloride | 13E15B40-297021  | 1       |
| Caelo                      | Propranolol hydrochloride | 13E15-B40        | 3       |
| Fagron                     | Propranolol hydrochloride | 13E15-B40        | 6       |
| Fagron                     | Propranolol hydrochloride | 13E15-B40-289355 | 10      |
| Caelo                      | Propranolol hydrochloride | 13E15-B40-289355 | 3       |
| Fagron                     | Propranolol hydrochloride | 13E15-B40-294297 | 6       |
| Alliance health            | Propranolol hydrochloride | 13E15-B40-294297 | 1       |
| Fagron                     | Propranolol hydrochloride | 13E15-B40-297021 | 4       |
| Gutenberg-Apotheke         | Propranolol hydrochloride | 13I13-N04        | 1       |
| Caelo                      | Propranolol hydrochloride | 13I13N04         | 1       |
| Fagron                     | Propranolol hydrochloride | 13I13-N04        | 1       |
| Euro OTC                   | Propranolol hydrochloride | 13I13-N04        | 1       |
| Gehe Kassel 26.06.2015     | Propranolol hydrochloride | 15082401         | 1       |
| Calo/AHD                   | Propranolol hydrochloride | 15082401         | 1       |
| Caelo                      | Propranolol hydrochloride | 15082401         | 8       |
| Caelo                      | Propranolol hydrochloride | 15082405         | 3       |
| Caelo                      | Propranolol hydrochloride | 15283301         | 8       |
| Caelo                      | Propranolol hydrochloride | 15283302         | 4       |
| Caelo                      | Propranolol hydrochloride | 15422501         | 6       |
| Caelo/Noweda               | Propranolol hydrochloride | 15283302         | 1       |
| Caelo                      | Propranolol hydrochloride | 15422502         | 8       |
| /O. Geilenkirchen          | Propranolol hydrochloride | 15422502         | 1       |
| Caelo                      | Propranolol hydrochloride | 15422505         | 3       |
| Fagron                     | Propranolol hydrochloride | 15F16-B02        | 1       |
| Caelo                      | Propranolol hydrochloride | 15F16-B02        | 1       |
| Changzhou Yabang Pharma... | Propranolol hydrochloride | 15F16-B02        | 1       |
| Caelo                      | Propranolol hydrochloride | 15F16-B02-312979 | 2       |
| Fagron                     | Propranolol hydrochloride | 15F16-B02-312979 | 3       |
| Fagron                     | Propranolol hydrochloride | 15F16B02312979   | 1       |
| Fagron                     | Propranolol hydrochloride | 15K11-B01-316401 | 7       |
| Fagron                     | Propranolol hydrochloride | 15K11-B01        | 1       |
| Caelo                      | Propranolol hydrochloride | 15K11-B01-316401 | 1       |
| Caelo                      | Propranolol hydrochloride | 16138304         | 1       |
| Caelo                      | Propranolol hydrochloride | 16E09-B09-326637 | 1       |
| Fagron                     | Propranolol hydrochloride | 16E09-B09-326637 | 1       |
| Inresa 22.09.15            | Propranolol hydrochloride | 3043PRRII        | 1       |
| Fagron                     | Propranolol hydrochloride | 28051508         | 1       |
| phönix                     | Propranolol hydrochloride | 2/AKD3           | 1       |
| Fagron                     | Propranolol hydrochloride | 3050PRII         | 1       |
| Fagron                     | Propranolol hydrochloride | 3913M-03609      | 1       |
| Fagron                     | Propranolol hydrochloride | 3112U-03609      | 1       |
| Fagron                     | Propranolol hydrochloride | 5101             | 1       |
| Fagron                     | Propranolol hydrochloride | 700556-0001      | 1       |

*continued on the next page*

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| Supplier                   | Substance                 | Batch        | Spectra |
|----------------------------|---------------------------|--------------|---------|
| Caelo                      | Propranolol hydrochloride | M130104      | 1       |
| Fagron                     | Propranolol hydrochloride | M130104      | 2       |
| Fagron                     | Propranolol hydrochloride | 402310015    | 1       |
| Löwen City-Apotheke Bar... | Propranolol hydrochloride | 4012013      | 1       |
| Caelo                      | Propranolol hydrochloride | m130104      | 1       |
| Fagron                     | Propranolol hydrochloride | 9L09-N06     | 1       |
| Caelo                      | Propranolol hydrochloride | 11F21-N11    | 3       |
| ANZAG am 10.05.2012        | Propranolol hydrochloride | 11L01-N05    | 1       |
| Fagron                     | Propranolol hydrochloride | 11I19-N09    | 1       |
| Noweda                     | Propranolol hydrochloride | 11L01-N05    | 1       |
| Caelo                      | Propranolol hydrochloride | 11L01-N05    | 1       |
| Fagron                     | Propranolol hydrochloride | 11L01-N05    | 2       |
| Caelo                      | Propranolol hydrochloride | 12370703     | 1       |
| Fagron                     | Propranolol hydrochloride | 12D27-N14    | 4       |
| Caelo                      | Propranolol hydrochloride | 12a27-n04    | 1       |
| Fagron                     | Propranolol hydrochloride | 12A27-N04    | 1       |
| Fagron                     | Propranolol hydrochloride | 12F29-N06    | 4       |
| Caelo                      | Propranolol hydrochloride | 12D27-N14    | 2       |
| Fagron                     | Propranolol hydrochloride | 12f29-n06    | 1       |
| Fagron                     | Propranolol hydrochloride | 12F29-N06    | 1       |
| Fagron                     | Propranolol hydrochloride | 12K06-N07    | 1       |
| Fagron                     | Propranolol hydrochloride | 12K06N07     | 1       |
| fragon/AHD                 | Propranolol hydrochloride | 13/13-N04    | 1       |
| Fagron                     | Propranolol hydrochloride | 13/13-N04    | 3       |
| Fagron                     | Propranolol hydrochloride | 20250711-8   | 1       |
| Fagron                     | Propranolol hydrochloride | 3050PRRII    | 1       |
| Noweda                     | Propranolol hydrochloride |              | 1       |
| Fagron                     | Propranolol hydrochloride | 31101201     | 1       |
| Fagron                     | Propranolol hydrochloride | 9CMK6AA71374 | 1       |
| Gehe                       | Propranolol hydrochloride |              | 1       |
| InfectoPharm               | Propranolol hydrochloride | J0512011     | 1       |
| InfectoPharm               | Propranolol hydrochloride | J051201      | 1       |
| Caelo                      | Propranolol hydrochloride | 12370707     | 1       |

- 69 433 spectra from 414 *Apo-Ident* customers from a total of 23 733 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Propranolol hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Propranolol hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 161           | 0              | 146 568       |
| <b>Type C</b> | 0              | 165           | 35             | 69 433        |

The substance/substance group *Propranolol hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.2733 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 82.5000 % (> 81.0000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 20954            | 20954                      | 0.00                                | 53.11                                  |
| 21396            | 20954                      | 7.62                                | 52.34                                  |
| 21410            | 20954                      | 5.46                                | 52.34                                  |
| 22591            | 20954                      | 6.48                                | 52.45                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Propyl-4-hydroxybenzoate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20981-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Propyl-4-hydroxybenzoate; Propylis parahydroxybenzoas; Propylum parahydroxybenzoicum

### Special notes

When selecting the *Propyl-4-hydroxybenzoate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Propyl-4-hydroxybenzoate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Propyl-4-hydroxy... | 11373523 | 20981     | 40      | 1402440     |
| Caelo    | Propyl-4-hydroxy... | 13365009 | 21758     | 40      | 20131203    |
| Caelo    | Propyl-4-hydroxy... | 162595   | 22754     | 40      | 20161005*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Propyl-4-hydroxybenzoate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 152 spectra of 5 reference samples from the substance/substance group *Propyl-4-hydroxybenzoate*.

| Supplier | Substance                | Batch    | Sample ID          | Spectra |
|----------|--------------------------|----------|--------------------|---------|
| Caelo    | Propyl-4-hydroxybenzoate | 10113716 | 20132              | 40      |
| Caelo    | Propyl-4-hydroxybenzoate | 13365009 | 21758 <sup>†</sup> | 20      |
| Caelo    | Propyl-4-hydroxybenzoate | 162595   | 22765              | 40      |
| Caelo    | Propyl-4-hydroxybenzoate | 171970   | 23675              | 40      |
| Caelo    | Propyl-4-hydroxybenzoate | 14359008 | not required       | 12      |

- 146 577 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 113 spectra from 84 *Apo-Ident* customers from 48 batches from the substance/substance group *Propyl-4-hydroxybenzoate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier                     | Substance                | Batch         | Spectra |
|------------------------------|--------------------------|---------------|---------|
| Caelo                        | Propyl-4-hydroxybenzoate | 11373523      | 3       |
| Caelo                        | Propyl-4-hydroxybenzoate | 13051504      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 3041408       | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 13100208      | 1       |
| PHOENIX 10.03.2014           | Propyl-4-hydroxybenzoate | 11373526      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 13100215      | 8       |
| Gehe 5.3.14                  | Propyl-4-hydroxybenzoate | 13100215      | 1       |
| Caesar &Loretz GmbH          | Propyl-4-hydroxybenzoate | 13100215      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 13100217      | 2       |
| Caelo                        | Propyl-4-hydroxybenzoate | 13100218      | 3       |
| Caelo                        | Propyl-4-hydroxybenzoate | 13365006      | 5       |
| Caelo                        | Propyl-4-hydroxybenzoate | 13100219      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 13365009      | 4       |
| Caelo                        | Propyl-4-hydroxybenzoate | 13365011      | 6       |
| Caelo                        | Propyl-4-hydroxybenzoate | 13365012      | 2       |
| Caelo                        | Propyl-4-hydroxybenzoate | 14359005      | 6       |
| Caelo                        | Propyl-4-hydroxybenzoate | 14359006      | 3       |
| Caelo                        | Propyl-4-hydroxybenzoate | 14359008      | 5       |
| Caelo                        | Propyl-4-hydroxybenzoate | 14359019      | 1       |
| Sanacorp                     | Propyl-4-hydroxybenzoate | 14359008      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 14359020      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 15246502      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 15246501      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 3115M-01931   | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 16259505      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 15276514      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 1913I-01931   | 1       |
| Caesar/Noweda                | Propyl-4-hydroxybenzoate | 3710M-01931   | 2       |
| Caelo                        | Propyl-4-hydroxybenzoate | 221014PAS01   | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 4314U-01931   | 1       |
| GATT-KOLLER/PHOENIX          | Propyl-4-hydroxybenzoate | 5080/11130214 | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 11102609      | 3       |
| Caelo                        | Propyl-4-hydroxybenzoate | 713Q-01931    | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 1108211931    | 1       |
| Fagron                       | Propyl-4-hydroxybenzoate | 610M-01931    | 1       |
| siehe WE-Prüfprotokoll       | Propyl-4-hydroxybenzoate | 84/11         | 1       |
| Sanacorp                     | Propyl-4-hydroxybenzoate | AKD3          | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 11102611      | 2       |
| Caelo                        | Propyl-4-hydroxybenzoate | 11102610      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 11102621      | 2       |
| Caelo                        | Propyl-4-hydroxybenzoate | 11102624      | 3       |
| Caelo                        | Propyl-4-hydroxybenzoate | 11373505      | 3       |
| Post-Apotheke                | Propyl-4-hydroxybenzoate | 11373505      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 11373504      | 1       |
| Noweda                       | Propyl-4-hydroxybenzoate | 11373505      | 2       |
| Caelo                        | Propyl-4-hydroxybenzoate | 11373512      | 6       |
| Anzag                        | Propyl-4-hydroxybenzoate | 11373512      | 2       |
| Caelo                        | Propyl-4-hydroxybenzoate | 11373518      | 3       |
| Caelo                        | Propyl-4-hydroxybenzoate | 113735223     | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 11373524      | 1       |
| AHD                          | Propyl-4-hydroxybenzoate | 11373523      | 1       |
| Herbasinica                  | Propyl-4-hydroxybenzoate | 11373523      | 1       |
| Phönix 14.01.2014            | Propyl-4-hydroxybenzoate | 11373526      | 1       |
| Phoenix                      | Propyl-4-hydroxybenzoate | 13100215      | 1       |
| Fagron                       | Propyl-4-hydroxybenzoate | 12B13-N04     | 1       |
| Euro OTC                     | Propyl-4-hydroxybenzoate | 2509025       | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 82792159      | 1       |
| Sanacorp, 12.08.2016, 4. . . | Propyl-4-hydroxybenzoate | 14359005      | 1       |
| Caelo                        | Propyl-4-hydroxybenzoate | 290114PML03   | 1       |

- 69 520 spectra from 414 *Apo-Ident* customers from a total of 23 755 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Propyl-4-hydroxybenzoate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Propyl-4-hydroxybenzoate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 142           | 10             | 146 577       |
| <b>Type C</b> | 0              | 111           | 2              | 69 520        |

The substance/substance group *Propyl-4-hydroxybenzoate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 93.4211 % (> 91.4474 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 98.2301 % (> 95.5752 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20981     | 20981               | 0.00                         | 25.72                           |
| 21758     | 20981               | 5.28                         | 23.55                           |
| 22754     | 22754               | 0.00                         | 20.15                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das

alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Propyphenazone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20805-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Propyphenazone; Propyphenazonum; Propyphenazonum plv.

### Special notes

When selecting the *Propyphenazone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Propyphenazone*:

| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate |
|----------|----------------|------------------|-----------|---------|-------------|
| Caelo    | Propyphenazone | 12039103         | 20805     | 40      | 1402051     |
| Caelo    | Propyphenazone | 13332206         | 21454     | 40      | 20131009    |
| Fagron   | Propyphenazone | 16E02-B08-327928 | 23261     | 40      | 20160602    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Propyphenazone*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *Propyphenazone*.

| Supplier | Substance      | Batch    | Sample ID          | Spectra |
|----------|----------------|----------|--------------------|---------|
| Caelo    | Propyphenazone | 9369110  | 20224              | 40      |
| Caelo    | Propyphenazone | 13332206 | 21454 <sup>†</sup> | 20      |
| Caelo    | Propyphenazone | 15348908 | 23254              | 40      |

- 146 629 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 21 spectra from 7 *Apo-Ident* customers from 14 batches from the substance/substance group *Propyphenazone*.

| Supplier                | Substance      | Batch    | Spectra |
|-------------------------|----------------|----------|---------|
| Raben-Apotheke Mildenau | Propyphenazone | 12039103 | 1       |
| Caelo                   | Propyphenazone | 13036702 | 4       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

continued from previous page

| Supplier              | Substance      | Batch            | Spectra |
|-----------------------|----------------|------------------|---------|
| Fagron                | Propyphenazone | 13B12-B02-297171 | 1       |
| Gatt-Koller / Phoenix | Propyphenazone | 419/02123112     | 1       |
| Fargon                | Propyphenazone | 11H31-N07        | 1       |
| Caelo                 | Propyphenazone | 12039112         | 1       |
| Euro OTC              | Propyphenazone |                  | 1       |
| Caelo                 | Propyphenazone | 12039101         | 2       |
| Caelo                 | Propyphenazone | 13137104         | 1       |
| Caelo                 | Propyphenazone | 13332205         | 3       |
| Caelo                 | Propyphenazone | 15122504         | 1       |
| Caelo                 | Propyphenazone | 15122502         | 1       |
| Caelo                 | Propyphenazone | 15122505         | 1       |
| Caelo                 | Propyphenazone | 15348902         | 1       |
| Caelo                 | Propyphenazone | 12039103         | 1       |

- 69 612 spectra from 414 *Apo-Ident* customers from a total of 23 787 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Propyphenazone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Propyphenazone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 100           | 0              | 146 629       |
| <b>Type C</b> | 0              | 20            | 1              | 69 612        |

The substance/substance group *Propyphenazone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 95.2381 % (> 80.9524 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20805     | 20805               | 0.00                         | 43.41                           |
| 21454     | 20805               | 7.06                         | 43.96                           |
| 23261     | 20805               | 5.98                         | 42.01                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Pyridoxal-5-phosphate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20830-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Pyridoxal-5-phosphate; Pyridoxali phosphas

### Special notes

When selecting the *Pyridoxal-5-phosphate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Pyridoxal-5-phosphate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Euro OTC | Pyridoxal-5-phos... | 1302029-01 | 20830     | 40      | 8897        |
| Euro OTC | Pyridoxal-5-phos... | 1701015    | 23133     | 40      | 20170220*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Pyridoxal-5-phosphate*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *Pyridoxal-5-phosphate*.

| Supplier | Substance             | Batch      | Sample ID | Spectra |
|----------|-----------------------|------------|-----------|---------|
| Euro OTC | Pyridoxal-5-phosphate | 1302029-01 | 21097     | 40      |
| Euro OTC | Pyridoxal-5-phosphate | 1701015-01 | 23276     | 40      |

- 146 649 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 4 spectra from 4 *Apo-Ident* customers from 4 batches from the substance/substance group *Pyridoxal-5-phosphate*.

| Supplier      | Substance             | Batch      | Spectra |
|---------------|-----------------------|------------|---------|
| Inresa Arznei | Pyridoxal-5-phosphate | 13100411   | 1       |
| Euro OTC      | Pyridoxal-5-phosphate | 1408002-01 | 1       |
| Euro OTC      | Pyridoxal-5-phosphate | 1701015-01 | 1       |
| Denk          | Pyridoxal-5-phosphate | C041402802 | 1       |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Pyridoxal-5-phosphate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Pyridoxal-5-phosphate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 4             | 0              | 69 629        |

The substance/substance group *Pyridoxal-5-phosphate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20830     | 20830               | 0.00                         | 48.29                           |
| 23133     | 23133               | 0.00                         | 46.50                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Labor-

prüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Pyridoxine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20440-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Pyridoxine hydrochloride; Pyridoxini hydrochloridum; Pyridoxini hydrochloridum

### Special notes

When selecting the *Pyridoxine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Pyridoxine hydrochloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Caelo    | Pyridoxine hydro... | 14262302   | 21675     | 40      | 20141002    |
| Euro OTC | Pyridoxine hydro... | 1401044-01 | 21678     | 40      | 20140221    |
| Euro OTC | Pyridoxine hydro... | 1407009-01 | 21773     | 40      | 20140807    |
| Euro OTC | Pyridoxine hydro... | 1507012    | 21846     | 40      | 20150721*   |
| Euro OTC | Pyridoxine hydro... | 1601039    | 22300     | 40      | 20160203*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Pyridoxine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 300 spectra of 10 reference samples from the substance/substance group *Pyridoxine hydrochloride*.

| Supplier | Substance                | Batch      | Sample ID          | Spectra |
|----------|--------------------------|------------|--------------------|---------|
| Fagron   | Pyridoxine hydrochloride | L12010105  | 20390              | 40      |
| Fagron   | Pyridoxine hydrochloride | 9I16-N14   | 20440              | 40      |
| Caelo    | Pyridoxine hydrochloride | 14262302   | 21675 <sup>†</sup> | 20      |
| Euro OTC | Pyridoxine hydrochloride | 1401044-01 | 21678 <sup>†</sup> | 20      |
| Euro OTC | Pyridoxine hydrochloride | 1407009-01 | 21773 <sup>†</sup> | 20      |
| Euro OTC | Pyridoxine hydrochloride | 1507012    | 21846 <sup>†</sup> | 20      |
| Euro OTC | Pyridoxine hydrochloride | 1601039    | 22300 <sup>†</sup> | 20      |
| Euro OTC | Pyridoxine hydrochloride | 1604063    | 22569              | 40      |
| Caelo    | Pyridoxine hydrochloride | 162225     | 22770              | 40      |
| Euro OTC | Pyridoxine hydrochloride | 1608035    | 22798              | 40      |

- 146 429 spectra from a total of 3184 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 46 spectra from 13 *Apo-Ident* customers from 25 batches from the substance/substance group *Pyridoxine hydrochloride*.

| Supplier                   | Substance                | Batch      | Spectra |
|----------------------------|--------------------------|------------|---------|
| Caelo                      | Pyridoxine hydrochloride | 15218709   | 1       |
| Euro OTC                   | Pyridoxine hydrochloride | 1110001-01 | 1       |
| Caelo                      | Pyridoxine hydrochloride | 13102509   | 2       |
| Caelo                      | Pyridoxine hydrochloride | 13102516   | 1       |
| Caelo                      | Pyridoxine hydrochloride | 14262302   | 3       |
| Euro OTC                   | Pyridoxine hydrochloride | 1407009-01 | 1       |
| Euro OTC                   | Pyridoxine hydrochloride | 1507012-01 | 1       |
| Caelo                      | Pyridoxine hydrochloride | 15218707   | 1       |
| Euro OTC                   | Pyridoxine hydrochloride | 1601039-01 | 1       |
| Caelo                      | Pyridoxine hydrochloride | 15218713   | 1       |
| Fagron                     | Pyridoxine hydrochloride | 9I16-N14   | 1       |
| Euro OTC                   | Pyridoxine hydrochloride | 1604063-01 | 1       |
| Caesar & Loretz GmbH, 4... | Pyridoxine hydrochloride | 11197009   | 5       |
| Caelo                      | Pyridoxine hydrochloride | 11021406   | 1       |
| Post-Apotheke              | Pyridoxine hydrochloride | 10026903   | 1       |
| Fagron                     | Pyridoxine hydrochloride | 11L19-N06  | 1       |
| Euro OTC                   | Pyridoxine hydrochloride | 1206022-02 | 1       |
| Caesar & Loretz GmbH, 4... | Pyridoxine hydrochloride | 12214102   | 5       |
| Caesar & Loretz GmbH, 4... | Pyridoxine hydrochloride | 12214110   | 2       |
| Caelo                      | Pyridoxine hydrochloride | 12214104   | 1       |
| Caelo                      | Pyridoxine hydrochloride | 12214110   | 2       |
| Caesar & Loretz GmbH, 4... | Pyridoxine hydrochloride | 12214115   | 7       |
| Caesar & Loretz GmbH, 4... | Pyridoxine hydrochloride | 12214119   | 2       |
| Fagron                     | Pyridoxine hydrochloride | 12e02-n02  | 1       |
| Euro OTC                   | Pyridoxine hydrochloride | 13D02-N04  | 1       |
| Fagron                     | Pyridoxine hydrochloride | L13080030  | 1       |

- 69 587 spectra from 414 *Apo-Ident* customers from a total of 23 776 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Pyridoxine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Pyridoxine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 284           | 16             | 146 429       |
| <b>Type C</b> | 0              | 43            | 3              | 69 587        |

The substance/substance group *Pyridoxine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 94.6667 % (> 93.6667 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 93.4783 % (> 86.9565 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21675            | 21846                      | 6.18                                | 69.97                                  |
| 21678            | 21846                      | 4.20                                | 68.98                                  |
| 21773            | 21846                      | 1.04                                | 68.19                                  |
| 21846            | 21846                      | 0.00                                | 68.11                                  |
| 22300            | 22300                      | 0.00                                | 67.74                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Quinidine sulfate dihydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20819-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Quinidine sulfate dihydrate; Chinidini sulfas; Quinidine sulphate dihydrate

### Special notes

When selecting the *Quinidine sulfate dihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Quinidine sulfate dihydrate*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Quinidine sulfat... | 12L04-N10        | 20819     | 40      | AR-14-FG-013249-01 |
| Fagron   | Quinidine sulfat... | 12J16-B03        | 21217     | 39      | 1412323            |
| Fagron   | Quinidine sulfat... | 14I04-B09-304357 | 21810     | 35      | AR-15-FG-015409-01 |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 114 spectra of 3 reference samples from the substance/substance group *Quinidine sulfate dihydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 272 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 175 spectra of 5 reference samples from the substance/substance group *Quinidine sulfate dihydrate*.

| Supplier | Substance                   | Batch            | Sample ID          | Spectra |
|----------|-----------------------------|------------------|--------------------|---------|
| Fagron   | Quinidine sulfate dihydrate | 11J11-N02        | 20375              | 40      |
| Fagron   | Quinidine sulfate dihydrate | 12E25-N03        | 20582              | 40      |
| Fagron   | Quinidine sulfate dihydrate | 12E25-N03        | 20604              | 40      |
| Fagron   | Quinidine sulfate dihydrate | 14I04-B09-304357 | 21810 <sup>†</sup> | 15      |
| Fagron   | Quinidine sulfate dihydrate | 16A06-B04-324954 | 22970              | 40      |

- 146 554 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Quinidine sulfate dihydrate*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Quinidine sulfate dihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Quinidine sulfate dihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 114           | 0              | 71 272        |
| <b>Type B</b> | 0              | 135           | 40             | 146 554       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Quinidine sulfate dihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.7368 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 77.1429 % (> 75.4286 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20819     | 20819               | 0.00                         | 28.82                           |
| 21217     | 21217               | 0.00                         | 27.17                           |
| 21810     | 21810               | 0.00                         | 28.68                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Quinine dihydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 23186-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Quinine dihydrochloride; Chinini dihydrochloridum; Chininum dihydrochloricum

### Special notes

When selecting the *Quinine dihydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Quinine dihydrochloride*:

| Supplier | Substance           | Batch  | Sample ID | Spectra | Certificate |
|----------|---------------------|--------|-----------|---------|-------------|
| Caelo    | Quinine dihydroc... | 172129 | 23636     | 40      | 20173008*   |
| Caelo    | Quinine dihydroc... | 172072 | 23655     | 40      | 20170830*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Quinine dihydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 3 reference samples from the substance/substance group *Quinine dihydrochloride*.

| Supplier | Substance               | Batch    | Sample ID | Spectra |
|----------|-------------------------|----------|-----------|---------|
| Caelo    | Quinine dihydrochloride | 16269603 | 23185     | 40      |
| Caelo    | Quinine dihydrochloride | 16269603 | 23186     | 40      |
| Caelo    | Quinine dihydrochloride | 162696   | 23358     | 40      |

- 146 609 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Quinine dihydrochloride*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Quinine dihydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Quinine dihydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 120           | 0              | 146 609       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Quinine dihydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 23636     | 23636               | 0.00                         | 84.43                           |
| 23655     | 23655               | 0.00                         | 83.49                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Quinine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20547-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Quinine hydrochloride; Chinini hydrochloridum; Chininum hydrochloricum

### Special notes

When selecting the *Quinine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Quinine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Quinine hydrochl... | 13G10-N07        | 21235     | 30      | 20130809           |
| Fagron   | Quinine hydrochl... | 13I30-B02-295630 | 21809     | 40      | AR-15-FG-015410-01 |
| Caelo    | Quinine hydrochl... | 15376201         | 22309     | 40      | 20151105           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 110 spectra of 3 reference samples from the substance/substance group *Quinine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 276 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 160 spectra of 5 reference samples from the substance/substance group *Quinine hydrochloride*.

| Supplier | Substance             | Batch            | Sample ID          | Spectra |
|----------|-----------------------|------------------|--------------------|---------|
| Fagron   | Quinine hydrochloride | 12C29-N04        | 20547              | 40      |
| Fagron   | Quinine hydrochloride | 13I30-B02-295630 | 21809 <sup>†</sup> | 20      |
| Caelo    | Quinine hydrochloride | 15376201         | 22309 <sup>†</sup> | 20      |
| Fagron   | Quinine hydrochloride | 15A20-B03-319027 | 23573              | 40      |
| Caelo    | Quinine hydrochloride | 16283302         | 23577              | 40      |

- 146 569 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 7 spectra from 7 *Apo-Ident* customers from 7 batches from the substance/substance group *Quinine hydrochloride*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier    | Substance             | Batch         | Spectra |
|-------------|-----------------------|---------------|---------|
| Caelo       | Quinine hydrochloride | 12316611      | 1       |
| Caelo       | Quinine hydrochloride | 12316604      | 1       |
| Caelo       | Quinine hydrochloride | 13D24-N06     | 1       |
| Fagron      | Quinine hydrochloride | 10N129B       | 1       |
| Fagron      | Quinine hydrochloride | 13G10-N07     | 1       |
| Gatt-Koller | Quinine hydrochloride | 3500/08103810 | 1       |
| Caelo       | Quinine hydrochloride | 12316605      | 1       |

- 69 626 spectra from 414 *Apo-Ident* customers from a total of 23 794 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Quinine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Quinine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 110           | 0              | 71 276        |
| <b>Type B</b> | 0              | 160           | 0              | 146 569       |
| <b>Type C</b> | 0              | 7             | 0              | 69 626        |

The substance/substance group *Quinine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.5455 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.2500 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21235     | 21809               | 9.62                         | 26.96                           |
| 21809     | 21809               | 0.00                         | 16.88                           |
| 22309     | 21809               | 5.86                         | 20.89                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Quinine sulfate dihydrate</b>                                |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 21057-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Quinine sulfate dihydrate; Chinini sulfas; Chininum sulfuricum; Quinine sulphate dihydrate

### Special notes

When selecting the *Quinine sulfate dihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Quinine sulfate dihydrate*:

| Supplier | Substance           | Batch     | Sample ID | Spectra | Certificate        |
|----------|---------------------|-----------|-----------|---------|--------------------|
| Fagron   | Quinine sulfate ... | 13J23-N03 | 21057     | 40      | 1404401            |
| Fagron   | Quinine sulfate ... | 14B27-B01 | 21277     | 40      | AR-16-FG-009455-01 |
| Caelo    | Quinine sulfate ... | 13024604  | 21429     | 40      | AR-16-FG-005472-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Quinine sulfate dihydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Quinine sulfate dihydrate*.

| Supplier | Substance                 | Batch    | Sample ID          | Spectra |
|----------|---------------------------|----------|--------------------|---------|
| Caelo    | Quinine sulfate dihydrate | 13024604 | 21429 <sup>†</sup> | 20      |
| Caelo    | Quinine sulfate dihydrate | 15230005 | 22959              | 40      |
| Caelo    | Quinine sulfate dihydrate | 170616   | 23281              | 40      |
| Caelo    | Quinine sulfate dihydrate | 170616   | 23316              | 40      |

- 146 589 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 3 spectra from 2 *Apo-Ident* customers from 3 batches from the substance/substance group *Quinine sulfate dihydrate*.

| Supplier | Substance                 | Batch          | Spectra |
|----------|---------------------------|----------------|---------|
| Caelo    | Quinine sulfate dihydrate | 15B06B03304359 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

continued from previous page

| Supplier              | Substance                 | Batch         | Spectra |
|-----------------------|---------------------------|---------------|---------|
| Gatt-Koller / Phoenix | Quinine sulfate dihydrate | 4928/11132214 | 1       |
| Gatt-Koller / Phoenix | Quinine sulfate dihydrate | 2503/07143314 | 1       |

- 69 630 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Quinine sulfate dihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Quinine sulfate dihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 140           | 0              | 146 589       |
| <b>Type C</b> | 0              | 3             | 0              | 69 630        |

The substance/substance group *Quinine sulfate dihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.7143 %) |
| <b>Type C</b> | 100.0000 % (> 99.8817 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21057     | 21057               | 0.00                         | 17.51                           |
| 21277     | 21277               | 0.00                         | 11.66                           |
| 21429     | 21429               | 0.00                         | 17.68                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Quinoline yellow**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20456-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Quinoline yellow

### Special notes

When selecting the *Quinoline yellow* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Quinoline yellow*:

| Supplier | Substance        | Batch     | Sample ID | Spectra | Certificate |
|----------|------------------|-----------|-----------|---------|-------------|
| Fagron   | Quinoline yellow | 12E24-N01 | 20731     | 40      | 20120601    |
| Caelo    | Quinoline yellow | 12042010  | 20922     | 40      | 20120314    |
| Caelo    | Quinoline yellow | 13109108  | 21305     | 40      | 1711481     |
| Caelo    | Quinoline yellow | 17034101  | 23400     | 40      | 1709327     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Quinoline yellow*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 210 spectra of 6 reference samples from the substance/substance group *Quinoline yellow*.

| Supplier    | Substance        | Batch     | Sample ID          | Spectra |
|-------------|------------------|-----------|--------------------|---------|
| Caelo       | Quinoline yellow | 11089608  | 20456              | 40      |
| Caelo       | Quinoline yellow | 11089608  | 20525              | 40      |
| zu erfassen | Quinoline yellow | pending   | 20574              | 40      |
| Fagron      | Quinoline yellow | 12E24-N01 | 20731 <sup>†</sup> | 20      |
| Caelo       | Quinoline yellow | 16050101  | 23401              | 40      |
| Caelo       | Quinoline yellow | 172277    | 23685              | 30      |

- 146 519 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 51 spectra from 36 *Apo-Ident* customers from 32 batches from the substance/substance group *Quinoline yellow*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier            | Substance        | Batch      | Spectra |
|---------------------|------------------|------------|---------|
| Caelo               | Quinoline yellow | 11089610   | 2       |
| Caelo               | Quinoline yellow | 13109102   | 2       |
| Caelo               | Quinoline yellow | 13109106   | 3       |
| Caelo               | Quinoline yellow | 13109109   | 1       |
| Fagron              | Quinoline yellow | 13C25-N15  | 2       |
| Caelo               | Quinoline yellow | 14049401   | 2       |
| Caelo               | Quinoline yellow | 14274305   | 1       |
| Caelo               | Quinoline yellow | 14274309   | 1       |
| Caelo               | Quinoline yellow | 14363201   | 1       |
| Caelo               | Quinoline yellow | 14363202   | 4       |
| Caelo               | Quinoline yellow | 14363207   | 1       |
| VDL;23.1.16;6,32EUR | Quinoline yellow | 15276801   | 1       |
| Caelo               | Quinoline yellow | 15276801   | 1       |
| Caelo               | Quinoline yellow | 16050101   | 1       |
| Caelo               | Quinoline yellow | 15276803   | 1       |
| Caelo               | Quinoline yellow | 713E-03146 | 1       |
| Fagron              | Quinoline yellow | 100427     | 1       |
| Caelo               | Quinoline yellow | 11089601   | 1       |
| Caelo               | Quinoline yellow | 11089606   | 1       |
| anzag am 06.07.2012 | Quinoline yellow | 11089608   | 1       |
| Caelo               | Quinoline yellow | 11089608   | 1       |
| Noweda              | Quinoline yellow | 11D13-N01  | 1       |
| Fagron              | Quinoline yellow | 11F30-N04  | 1       |
| Fagron              | Quinoline yellow | 11K08-N01  | 2       |
| Caelo               | Quinoline yellow | 12042002   | 3       |
| Caelo               | Quinoline yellow | 12042004   | 2       |
| PHOENIX             | Quinoline yellow | 12042004   | 1       |
| Caelo               | Quinoline yellow | 12042007   | 4       |
| Caelo               | Quinoline yellow | 12042010   | 1       |
| Fagron              | Quinoline yellow | 12B08-N08  | 1       |
| Fagron              | Quinoline yellow | 12E24-N05  | 1       |
| Fagron              | Quinoline yellow | 12L11-N07  | 1       |
| Caelo               | Quinoline yellow | 18011305   | 1       |
| Caelo               | Quinoline yellow | 20301211-6 | 1       |
| Fagron              | Quinoline yellow | 9878       | 1       |

- 69 582 spectra from 414 *Apo-Ident* customers from a total of 23 769 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Quinoline yellow* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Quinoline yellow* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 121           | 39             | 71 226        |
| Type B | 0              | 110           | 100            | 146 519       |
| Type C | 0              | 32            | 19             | 69 582        |

The substance/substance group *Quinoline yellow* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b> |
|---------------|--------------------------|-------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 75.6250 % (> 73.7500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 52.3810 % (> 50.9524 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 62.7451 % (> 56.8627 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 20731            | 21305                      | 29.11                               | 75.54                                  |
| 20922            | 21305                      | 5.54                                | 89.73                                  |
| 21305            | 21305                      | 0.00                                | 91.32                                  |
| 23400            | 23400                      | 0.00                                | 73.67                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | Quinolinol sulfate potassium sulfate                            |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20573-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

## Relevant substance names

Quinolinol sulfate potassium sulfate; Chinolini et kalii sulfas; Kalii oxychinolinum sulfuricum; Quinolinol sulphate potassium sulphate

## Special notes

When selecting the *Quinolinol sulfate potassium sulfate* substance/substance group, the following information is displayed to the user:

- Advice for the distinction from 8-hydroxyquinoline sulfate: 8-hydroxyquinoline sulfate is a spectrally similar substance, which is however currently not deliverable in Germany. Please decide, if an additional prove seems to be useful.

## Applicable documents

|                   |                                                            |
|-------------------|------------------------------------------------------------|
| 978-3-7692-5416-7 | European Pharmacopoeia 8th Edition, Basic Version 2014 [3] |
| Komm2.2.40        | Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident [4]          |
| AA004             | Erstellung und Validierung eines IdentModul-Updates        |
| Anhang F          | Zusatz zu den Modellen der zweiten Stufe                   |

## Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

## Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Quinolinol sulfate potassium sulfate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Quinolinol sulfa... | 13071104 | 20983     | 40      | 1403095     |
| Caelo    | Quinolinol sulfa... | 13403501 | 21430     | 40      | 20131218    |
| Caelo    | Quinolinol sulfa... | 15147704 | 22606     | 40      | 20150618    |
| Caelo    | Quinolinol sulfa... | 162218   | 22626     | 40      | 20160808*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Quinolinol sulfate potassium sulfate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Quinolinol sulfate potassium sulfate*.

| Supplier   | Substance                       | Batch    | Sample ID          | Spectra |
|------------|---------------------------------|----------|--------------------|---------|
| Dermapharm | Quinolinol sulfate potassium... | 71101    | 20168              | 40      |
| mibe GmbH  | Quinolinol sulfate potassium... | 100804   | 20573              | 40      |
| Caelo      | Quinolinol sulfate potassium... | 13403501 | 21430 <sup>†</sup> | 20      |
| Caelo      | Quinolinol sulfate potassium... | 15147704 | 22607              | 40      |
| Caelo      | Quinolinol sulfate potassium... | 16221809 | 23563              | 40      |

- 146 549 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 143 spectra from 68 *Apo-Ident* customers from 24 batches from the substance/substance group *Quinolinol sulfate potassium sulfate*.

| Supplier                | Substance                       | Batch       | Spectra |
|-------------------------|---------------------------------|-------------|---------|
| Fagron                  | Quinolinol sulfate potassium... | 10F01-N15   | 1       |
| Caelo                   | Quinolinol sulfate potassium... | 140804      | 4       |
| Dermapharm              | Quinolinol sulfate potassium... | 100804      | 9       |
| Phönix Gotha            | Quinolinol sulfate potassium... | 120905      | 4       |
| Caelo                   | Quinolinol sulfate potassium... | 13071104    | 3       |
| Nachprüfung             | Quinolinol sulfate potassium... | 13071104    | 2       |
| Caelo                   | Quinolinol sulfate potassium... | 13071106    | 1       |
| Caelo                   | Quinolinol sulfate potassium... | 13403501    | 6       |
| Caelo                   | Quinolinol sulfate potassium... | 13403506    | 9       |
| Caelo                   | Quinolinol sulfate potassium... | 13403513    | 1       |
| Dermapharm              | Quinolinol sulfate potassium... | 140804      | 32      |
| Dermapharm              | Quinolinol sulfate potassium... | 140804      | 1       |
| Fagron                  | Quinolinol sulfate potassium... | 140804      | 2       |
| Caelo                   | Quinolinol sulfate potassium... | 15147701    | 1       |
| Caelo                   | Quinolinol sulfate potassium... | 15147704    | 1       |
| Caelo                   | Quinolinol sulfate potassium... | 15147706    | 1       |
| Ebert-Jacobi            | Quinolinol sulfate potassium... | 16221804    | 1       |
| Dermapharm              | Quinolinol sulfate potassium... | 120905      | 37      |
| Caelo                   | Quinolinol sulfate potassium... | 13071101    | 2       |
| Nachprüfung             | Quinolinol sulfate potassium... | 2812U03423  | 1       |
| Caelo                   | Quinolinol sulfate potassium... | 2210E-03423 | 1       |
| Fagron                  | Quinolinol sulfate potassium... | 13G10-N06   | 1       |
| Nachprüfung             | Quinolinol sulfate potassium... | 120905      | 2       |
| Dermapharm AG/Noweda    | Quinolinol sulfate potassium... | 140804      | 1       |
| Phönix Gotha            | Quinolinol sulfate potassium... | 140804      | 1       |
| Pharmachen              | Quinolinol sulfate potassium... | 140804      | 1       |
| Geilenkirchen/Dermopham | Quinolinol sulfate potassium... | 140804      | 1       |
| Dermapharm              | Quinolinol sulfate potassium... | 1470804     | 1       |
| Stumpf                  | Quinolinol sulfate potassium... | 100804      | 1       |
| Fiebig ek: 5,68EUR      | Quinolinol sulfate potassium... | 100804      | 2       |
| Phönix Gotha            | Quinolinol sulfate potassium... | 100804      | 2       |
| Caelo                   | Quinolinol sulfate potassium... | 120905      | 1       |
| Gehe                    | Quinolinol sulfate potassium... | 120905      | 1       |
| Mibe                    | Quinolinol sulfate potassium... | 120905      | 1       |
| dermopharm/Noweda       | Quinolinol sulfate potassium... | 120905      | 1       |
| Caelo                   | Quinolinol sulfate potassium... | 82716049    | 1       |
| Caelo                   | Quinolinol sulfate potassium... | 7051305     | 1       |
| Caelo                   | Quinolinol sulfate potassium... | 9106304     | 1       |
| Caelo                   | Quinolinol sulfate potassium... | 10281601    | 1       |
| Caelo                   | Quinolinol sulfate potassium... | 10281607    | 1       |
| Gehe                    | Quinolinol sulfate potassium... | 10281609    | 1       |

- 69 490 spectra from 414 *Apo-Ident* customers from a total of 23 782 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Quinolinol sulfate potassium - sulfate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*.



For this purpose, all relevant spectra of the various substances were compared with *Quinolinol sulfate potassium sulfate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 160           | 0              | 71 226        |
| Type B | 0              | 140           | 40             | 146 538       |
| Type C | 0              | 77            | 66             | 69 477        |

The substance/substance group *Quinolinol sulfate potassium sulfate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| Type B | 100.0000 % (> 99.9923 %) | 77.7778 % (> 76.1111 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 53.8462 % (> 51.7483 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20983     | 20983               | 0.00                         | 59.32                           |
| 21430     | 22626               | 20.29                        | 66.41                           |
| 22606     | 22626               | 2.85                         | 67.79                           |
| 22626     | 22626               | 0.00                         | 69.01                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Resocrinol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20938-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Resocrinol; Resorcinolum

### Special notes

When selecting the *Resocrinol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Resocrinol*:

| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate        |
|----------|------------|------------------|-----------|---------|--------------------|
| Fagron   | Resocrinol | 12G24-N04        | 20938     | 40      | 1401462            |
| Caelo    | Resocrinol | 13293108         | 21471     | 40      | AR-15-FG-006906-01 |
| Fagron   | Resocrinol | 13I18-B09-291533 | 21706     | 30      | 20130606           |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 110 spectra of 3 reference samples from the substance/substance group *Resocrinol*. These samples are listed above in the [calibration samples](#) section.
- 71 276 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 115 spectra of 4 reference samples from the substance/substance group *Resocrinol*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Fagron   | Resocrinol | 11A19-N09        | 20240              | 40      |
| Caelo    | Resocrinol | 13293108         | 21471 <sup>†</sup> | 20      |
| Fagron   | Resocrinol | 13I18-B09-291533 | 21706 <sup>†</sup> | 15      |
| Caelo    | Resocrinol | 161533           | 22632              | 40      |

- 146 614 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 111 spectra from 75 *Apo-Ident* customers from 53 batches from the substance/substance group *Resocrinol*.

| Supplier | Substance  | Batch    | Spectra |
|----------|------------|----------|---------|
| Caelo    | Resocrinol | 10218809 | 2       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier         | Substance  | Batch            | Spectra |
|------------------|------------|------------------|---------|
| Caelo            | Resocrinol | 11d29-n14        | 2       |
| Fargon           | Resocrinol | 11D29-2011       | 1       |
| Fargon           | Resocrinol | 11/13-no2        | 1       |
| Gehe             | Resocrinol | 11L13-N02        | 1       |
| Fargon           | Resocrinol | 1112013A         | 1       |
| Caelo            | Resocrinol | 2041512          | 1       |
| Caelo            | Resocrinol | 10111210         | 1       |
| Phönix Gotha     | Resocrinol | 10218802         | 1       |
| Fargon           | Resocrinol | 11/13-N02        | 3       |
| Euro OTC         | Resocrinol | 11/13-N02        | 1       |
| Caelo            | Resocrinol | 11309602         | 1       |
| Caelo            | Resocrinol | 11309610         | 4       |
| Fargon           | Resocrinol | 11A19-N09        | 1       |
| Fargon           | Resocrinol | 11L19-N19        | 4       |
| Caelo            | Resocrinol | 11A19-N09        | 1       |
| Fargon           | Resocrinol | 12/16010         | 1       |
| Caelo            | Resocrinol | 12255614         | 2       |
| Fargon           | Resocrinol | 12G24-N004       | 1       |
| Fargon           | Resocrinol | 12G24-N04        | 10      |
| Anzag 08.02.2013 | Resocrinol | 12G24-N04        | 1       |
| Caelo            | Resocrinol | 12G24-N04        | 2       |
| vdl              | Resocrinol | 12G24-N04        | 1       |
| Gehe             | Resocrinol | 12G24-N04        | 1       |
| Gehe             | Resocrinol | 12G-24-N04       | 1       |
| Gehe 16.06.2013  | Resocrinol | 12G24-N04        | 1       |
| Euro OTC         | Resocrinol | 12g24-n04        | 1       |
| Fargon           | Resocrinol | 12g24-N04        | 1       |
| Fargon           | Resocrinol | 12K30-N03        | 5       |
| anzag 13.09.13   | Resocrinol | 12K30N30         | 1       |
| Fargon           | Resocrinol | 13/17071         | 1       |
| Fargon           | Resocrinol | 13/18-B09-291534 | 1       |
| Caelo            | Resocrinol | 13/18-B09291534  | 1       |
| Caelo            | Resocrinol | 13/18-B19-291534 | 1       |
| Noweda           | Resocrinol | 1318b09291533    | 1       |
| Caelo            | Resocrinol | 13293103         | 1       |
| Caelo            | Resocrinol | 13293110         | 1       |
| Caelo            | Resocrinol | 13293115         | 1       |
| Fargon           | Resocrinol | 13E24-N10        | 10      |
| Gehe             | Resocrinol | 13E24-N10        | 1       |
| Noweda           | Resocrinol | 13E24-N10        | 1       |
| Fargon           | Resocrinol | 13I18-B09        | 2       |
| Fargon           | Resocrinol | 14G10B06         | 1       |
| Fargon           | Resocrinol | 14/19050         | 1       |
| Fargon           | Resocrinol | 14/16062         | 1       |
| Fargon           | Resocrinol | 13I18-B09-291533 | 1       |
| Phoenix goettin  | Resocrinol | 13I18-B09-291534 | 1       |
| Fargon           | Resocrinol | 14G10-B06        | 1       |
| Fargon           | Resocrinol | 14G10-B06-296296 | 4       |
| Phönix Gotha     | Resocrinol | 14G10-B06-296296 | 1       |
| Fargon           | Resocrinol | 14G10-B06-296297 | 3       |
| Fargon           | Resocrinol | 14J15-B02        | 1       |
| Fargon           | Resocrinol | 14J15-B02-307749 | 4       |
| Caelo            | Resocrinol | 15009507         | 4       |
| Caelo            | Resocrinol | 15009502         | 1       |
| Caelo            | Resocrinol | 15009511         | 1       |
| Fargon           | Resocrinol | 15K24-B02-317584 | 2       |
| Caelo            | Resocrinol | 19061305         | 1       |
| Fargon           | Resocrinol | 2112I-02170      | 1       |
| Fargon           | Resocrinol | 16D29-B01-323046 | 1       |
| Caelo            | Resocrinol | 206370-0003      | 1       |

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| Supplier | Substance  | Batch            | Spectra |
|----------|------------|------------------|---------|
| Fagron   | Resocrinol | 16D29-B01-329760 | 1       |
| Caelo    | Resocrinol | 5052             | 1       |
| GEHE     | Resocrinol | 11L19-N19        | 1       |

- 69 522 spectra from 414 *Apo-Ident* customers from a total of 23 750 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Resocrinol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Resocrinol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 110           | 0              | 71 276        |
| <b>Type B</b> | 0              | 115           | 0              | 146 614       |
| <b>Type C</b> | 0              | 110           | 1              | 69 522        |

The substance/substance group *Resocrinol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.5455 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.7826 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 99.0991 % (> 96.3964 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20938     | 20938               | 0.00                         | 37.89                           |
| 21471     | 21471               | 0.00                         | 33.09                           |
| 21706     | 21471               | 4.96                         | 26.08                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ribavirin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22346-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ribavirin; Ribavirinum

### Special notes

When selecting the *Ribavirin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ribavirin*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate        |
|----------|-----------|------------|-----------|---------|--------------------|
| Euro OTC | Ribavirin | 1304027-01 | 22346     | 30      | AR-16-FG-007485-01 |
| Euro OTC | Ribavirin | 1308001    | 22382     | 30      | 20130902*          |
| Euro OTC | Ribavirin | 1604012    | 22528     | 40      | 20160428*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 100 spectra of 3 reference samples from the substance/substance group *Ribavirin*. These samples are listed above in the [calibration samples](#) section.
- 71 286 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 70 spectra of 3 reference samples from the substance/substance group *Ribavirin*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Euro OTC | Ribavirin | 1304027-01 | 22346 <sup>†</sup> | 15      |
| Euro OTC | Ribavirin | 1308001    | 22382 <sup>†</sup> | 15      |
| Euro OTC | Ribavirin | 1304027-02 | 23023              | 40      |

- 146 659 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Ribavirin*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ribavirin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ribavirin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 100           | 0              | 71 286        |
| <b>Type B</b> | 0              | 70            | 0              | 146 659       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Ribavirin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 91.4286 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22346     | 22346               | 0.00                         | 24.73                           |
| 22382     | 22382               | 0.00                         | 30.08                           |
| 22528     | 22528               | 0.00                         | 19.15                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Riboflavin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20409-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Riboflavin; Riboflavinum

### Special notes

When selecting the *Riboflavin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Riboflavin*:

| Supplier  | Substance  | Batch            | Sample ID | Spectra | Certificate        |
|-----------|------------|------------------|-----------|---------|--------------------|
| Fagron    | Riboflavin | 13D02-N03        | 20825     | 40      | AR-15-FG-000733-01 |
| AppliChem | Riboflavin | 3E003567         | 20893     | 40      | 20130128           |
| Caelo     | Riboflavin | 12003317         | 20925     | 40      | 1405155            |
| Caelo     | Riboflavin | 13305203         | 21389     | 40      | AR-15-FG-005686-01 |
| Fagron    | Riboflavin | 15G20-B13-310997 | 21955     | 40      | 20150819           |

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| Supplier | Substance  | Batch            | Sample ID | Spectra | Certificate        |
|----------|------------|------------------|-----------|---------|--------------------|
| Caelo    | Riboflavin | 14322008         | 22492     | 40      | AR-16-FG-013669-01 |
| Fagron   | Riboflavin | 16B18-B06-319026 | 22655     | 40      | AR-16-FG-014466-01 |
| Euro OTC | Riboflavin | 1701050          | 23004     | 40      | 20170214*          |
| Fagron   | Riboflavin | 17G14-B05-337885 | 23714     | 40      | AR-18-FG-000141-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 360 spectra of 9 reference samples from the substance/substance group *Riboflavin*. These samples are listed above in the [calibration samples](#) section.
- 71 026 spectra from a total of 1543 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 430 spectra of 12 reference samples from the substance/substance group *Riboflavin*.

| Supplier | Substance  | Batch            | Sample ID          | Spectra |
|----------|------------|------------------|--------------------|---------|
| Fagron   | Riboflavin | 10F23-N06        | 20409              | 40      |
| Fagron   | Riboflavin | 11L29-N01        | 20581              | 40      |
| Fagron   | Riboflavin | 11L29-N01        | 20587              | 40      |
| Fagron   | Riboflavin | pending          | 20609              | 40      |
| Fagron   | Riboflavin | 10F23-N06        | 20641              | 30      |
| Fagron   | Riboflavin | 13D02-N03        | 20914              | 40      |
| Caelo    | Riboflavin | 13305203         | 21389 <sup>†</sup> | 20      |
| Fagron   | Riboflavin | 15G20-B13-310997 | 21955 <sup>†</sup> | 20      |
| Euro OTC | Riboflavin | 1701050-01       | 23091              | 40      |
| Caelo    | Riboflavin | 15330708         | 23579              | 40      |
| Euro OTC | Riboflavin | 1707017          | 23612              | 40      |
| Caelo    | Riboflavin | 172722           | 23649              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 299 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 23 spectra from 14 *Apo-Ident* customers from 18 batches from the substance/substance group *Riboflavin*.

| Supplier                | Substance  | Batch            | Spectra |
|-------------------------|------------|------------------|---------|
| Fagron                  | Riboflavin | 12H30-N02        | 1       |
| Fagron                  | Riboflavin | 11L29-N01        | 1       |
| Fagron                  | Riboflavin | 12J17-N07        | 2       |
| Fagron                  | Riboflavin | 6120             | 1       |
| Vdl 09.05.14;Preis 7,45 | Riboflavin | 13305203/15R05   | 1       |
| Fagron                  | Riboflavin | 13J29-B04-287534 | 1       |
| Fagron                  | Riboflavin | 13J29-B04-287533 | 1       |
| Fagron                  | Riboflavin | 14B03-B07-292071 | 2       |
| Fagron                  | Riboflavin | 14B03B07292071   | 1       |
| Fagron                  | Riboflavin | 14K03-B04-304718 | 1       |
| Fagron                  | Riboflavin | 15G20-B13-310997 | 2       |
| Fagron                  | Riboflavin | 14E01-B10-296718 | 1       |
| Fagron                  | Riboflavin | 15I09-B02-315216 | 1       |
| Fagron                  | Riboflavin | 16B18b06319026   | 1       |
| Euro OTC                | Riboflavin | L1210048-01      | 1       |
| Fagron                  | Riboflavin | 11K02-N01        | 1       |
| Fagron                  | Riboflavin | 167720-0005      | 2       |
| Euro OTC                | Riboflavin | L1305039-01      | 2       |

- 69 610 spectra from 414 *Apo-Ident* customers from a total of 23 784 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Riboflavin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Riboflavin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 360           | 0              | 71 026        |
| <b>Type B</b> | 0              | 387           | 43             | 146 299       |
| <b>Type C</b> | 0              | 22            | 1              | 69 610        |

The substance/substance group *Riboflavin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.3333 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 90.0000 % (> 89.3023 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 95.6522 % (> 82.6087 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 20825            | 20825                      | 0.00                                | 17.50                                  |
| 20893            | 22492                      | 9.41                                | 20.78                                  |
| 20925            | 20925                      | 0.00                                | 19.74                                  |
| 21389            | 21389                      | 0.00                                | 16.59                                  |
| 21955            | 21389                      | 6.03                                | 17.76                                  |
| 22492            | 22492                      | 0.00                                | 27.25                                  |
| 22655            | 22655                      | 0.00                                | 21.46                                  |
| 23004            | 23004                      | 0.00                                | 14.94                                  |
| 23714            | 23714                      | 0.00                                | 21.35                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Riboflavin phosphate sodium**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20948-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Riboflavin phosphate sodium; Natrii lactoflavini phosphoricum; Riboflavini natrii phosphas

### Special notes

When selecting the *Riboflavin phosphate sodium* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Riboflavin phosphate sodium*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Riboflavin phosp... | 13I26-N06        | 20948     | 40      | 1403705            |
| Fagron   | Riboflavin phosp... | 15J02-B03-313137 | 22269     | 40      | AR-16-FG-009883-02 |
| Fagron   | Riboflavin phosp... | 17A03-B01-335897 | 23713     | 40      | AR-18-FG-000920-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Riboflavin phosphate sodium*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 65 spectra of 2 reference samples from the substance/substance group *Riboflavin phosphate sodium*.

| Supplier | Substance                   | Batch            | Sample ID          | Spectra |
|----------|-----------------------------|------------------|--------------------|---------|
| Fagron   | Riboflavin phosphate sodium | 14J31-B07-300519 | 21707              | 45      |
| Fagron   | Riboflavin phosphate sodium | 15J02-B03-313137 | 22269 <sup>†</sup> | 20      |

- 146 664 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 6 spectra from 2 *Apo-Ident* customers from 5 batches from the substance/substance group *Riboflavin phosphate sodium*.

| Supplier | Substance                   | Batch     | Spectra |
|----------|-----------------------------|-----------|---------|
| Fagron   | Riboflavin phosphate sodium | 12k07-N12 | 1       |
| Fagron   | Riboflavin phosphate sodium | 13126-N06 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



continued from previous page

| Supplier | Substance                   | Batch     | Spectra |
|----------|-----------------------------|-----------|---------|
| Fagron   | Riboflavin phosphate sodium | 15J02-B03 | 1       |
| Fagron   | Riboflavin phosphate sodium | 11G15-N06 | 2       |
| Fagron   | Riboflavin phosphate sodium | 11K24-N01 | 1       |

- 69 627 spectra from 414 *Apo-Ident* customers from a total of 23 796 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Riboflavin phosphate sodium* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Riboflavin phosphate sodium* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 65            | 0              | 146 664       |
| <b>Type C</b> | 0              | 6             | 0              | 69 627        |

The substance/substance group *Riboflavin phosphate sodium* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.7692 %) |
| <b>Type C</b> | 100.0000 % (> 99.8815 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20948     | 20948               | 0.00                         | 17.42                           |
| 22269     | 22269               | 0.00                         | 13.43                           |
| 23713     | 23713               | 0.00                         | 28.87                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Saccharin sodium**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20200-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Saccharin sodium; Saccharinum natricum; Saccharinum solubile; Sodium saccharin

### Special notes

When selecting the *Saccharin sodium* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Saccharin sodium*:

| Supplier | Substance        | Batch            | Sample ID | Spectra | Certificate        |
|----------|------------------|------------------|-----------|---------|--------------------|
| Fagron   | Saccharin sodium | 13I20-B06-291654 | 23020     | 40      | AR-17-FG-012457-01 |
| Fagron   | Saccharin sodium | 14F30-B02-296322 | 23452     | 40      | AR-17-FG-022421-01 |
| Fagron   | Saccharin sodium | 14F30-B02-296322 | 23453     | 40      | 20140711           |
| Caelo    | Saccharin sodium | 172110           | 23643     | 40      | 20170831*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Saccharin sodium*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 3 reference samples from the substance/substance group *Saccharin sodium*.

| Supplier | Substance        | Batch     | Sample ID | Spectra |
|----------|------------------|-----------|-----------|---------|
| Caelo    | Saccharin sodium | 10170511  | 20200     | 40      |
| Fagron   | Saccharin sodium | 12E03-N01 | 20482     | 40      |
| Caelo    | Saccharin sodium | 15087704  | 22769     | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 78 spectra from 62 *Apo-Ident* customers from 41 batches from the substance/substance group *Saccharin sodium*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier                   | Substance        | Batch         | Spectra |
|----------------------------|------------------|---------------|---------|
| Caelo                      | Saccharin sodium | 13205411      | 1       |
| Caelo                      | Saccharin sodium | 13205414      | 2       |
| Caesar & Loretz GmbH Hi... | Saccharin sodium | 13205418      | 2       |
| Caelo                      | Saccharin sodium | 14029705      | 5       |
| Caelo                      | Saccharin sodium | 1402970       | 1       |
| Caelo                      | Saccharin sodium | 14029707      | 2       |
| Caelo                      | Saccharin sodium | 14029709      | 1       |
| Sana 03.11.14 EK 3,95      | Saccharin sodium | 14029707      | 1       |
| Caelo                      | Saccharin sodium | 14029710      | 2       |
| Caelo                      | Saccharin sodium | 14213402      | 3       |
| Caelo                      | Saccharin sodium | 14213405      | 3       |
| Caelo                      | Saccharin sodium | 15084101      | 2       |
| Caelo                      | Saccharin sodium | 15087703      | 5       |
| Caelo                      | Saccharin sodium |               | 1       |
| Caelo                      | Saccharin sodium | 15087704      | 5       |
| Cael Sanacorp 05.02.2016   | Saccharin sodium | 15087703      | 1       |
| Jenne                      | Saccharin sodium | 15087707      | 1       |
| Euro OTC                   | Saccharin sodium | 15087704      | 1       |
| Caelo                      | Saccharin sodium | 15087713      | 6       |
| Caelo                      | Saccharin sodium | 16221010      | 1       |
| Caelo                      | Saccharin sodium | 16221005      | 2       |
| Caelo                      | Saccharin sodium | 21092015A     | 1       |
| Caelo                      | Saccharin sodium | 3131-02206    | 1       |
| Caelo                      | Saccharin sodium | 11025605      | 1       |
| Caelo                      | Saccharin sodium | 11025610      | 1       |
| Caelo                      | Saccharin sodium | 10170504      | 1       |
| Caelo                      | Saccharin sodium | 11172805      | 3       |
| Caelo                      | Saccharin sodium | 11172814      | 1       |
| Caelo                      | Saccharin sodium | 12362607      | 3       |
| Fagron                     | Saccharin sodium |               | 1       |
| Caelo                      | Saccharin sodium | 1236207       | 1       |
| Caelo                      | Saccharin sodium | 12139803      | 1       |
| Fagron                     | Saccharin sodium | 12A13-N03     | 1       |
| Fagron                     | Saccharin sodium | 12K26-N09     | 1       |
| Fagron                     | Saccharin sodium | 13D19-N01     | 3       |
| Fagron                     | Saccharin sodium | 12E03-N01     | 1       |
| Caelo                      | Saccharin sodium | 12C08-N08     | 1       |
| Fargon                     | Saccharin sodium | 12A13-N03     | 1       |
| Fagron                     | Saccharin sodium | 12F19-N039/16 | 1       |
| Caelo                      | Saccharin sodium | 90542309      | 1       |
| Fagron                     | Saccharin sodium | SH203/11      | 1       |
| Phönix Gotha               | Saccharin sodium | 1I12-N04      | 1       |
| Caesar&loretz,Phoenix      | Saccharin sodium | 15084101      | 1       |
| Caelo                      | Saccharin sodium | 82885059      | 1       |
| Caelo                      | Saccharin sodium | 13205408      | 1       |

- 69 555 spectra from 414 *Apo-Ident* customers from a total of 23 760 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Saccharin sodium* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Saccharin sodium* and it was

evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 160           | 0              | 71 226        |
| Type B | 0              | 36            | 84             | 146 609       |
| Type C | 0              | 27            | 51             | 69 555        |

The substance/substance group *Saccharin sodium* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| Type B | 100.0000 % (> 99.9923 %) | 30.0000 % (> 27.5000 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 34.6154 % (> 30.7692 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 23020     | 23020               | 0.00                         | 71.20                           |
| 23452     | 23452               | 0.00                         | 85.67                           |
| 23453     | 23452               | 34.23                        | 81.17                           |
| 23643     | 23643               | 0.00                         | 74.64                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Salbutamol sulfate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20476-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Salbutamol sulfate; Salbutamol sulphate; Salbutamoli sulfas; Salbutamolum sulfuricum

### Special notes

When selecting the *Salbutamol sulfate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Salbutamol sulfate*:

| Supplier | Substance          | Batch     | Sample ID | Spectra | Certificate        |
|----------|--------------------|-----------|-----------|---------|--------------------|
| Fagron   | Salbutamol sulfate | 11L21-N10 | 20476     | 40      | AR-13-FG-001850-01 |
| Fagron   | Salbutamol sulfate | 13K12-N02 | 21691     | 40      | 20131114           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Salbutamol sulfate*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Salbutamol sulfate*.

| Supplier | Substance          | Batch     | Sample ID          | Spectra |
|----------|--------------------|-----------|--------------------|---------|
| Fagron   | Salbutamol sulfate | 13K12-N02 | 21691 <sup>†</sup> | 20      |
| Fagron   | Salbutamol sulfate | 13K12-N02 | 23231              | 40      |
| Fagron   | Salbutamol sulfate | 13K12-N02 | 23232              | 40      |
| Fagron   | Salbutamol sulfate | 13K12-N02 | 23454              | 40      |
| Fagron   | Salbutamol sulfate | 13K12-N02 | 23455              | 40      |

- 146 549 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Salbutamol sulfate*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier | Substance          | Batch     | Spectra |
|----------|--------------------|-----------|---------|
| Noweda   | Salbutamol sulfate | 13K12-N02 | 1       |

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Salbutamol sulfate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Salbutamol sulfate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 180           | 0              | 146 549       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Salbutamol sulfate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.6667 %) |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20476     | 20476               | 0.00                         | 44.78                           |
| 21691     | 20476               | 19.09                        | 47.98                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Salicylic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20015-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Salicylic acid; Acidum salicylicum

### Special notes

When selecting the *Salicylic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Salicylic acid*:

| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate |
|----------|----------------|------------------|-----------|---------|-------------|
| Euro OTC | Salicylic acid | 1110020-01       | 20696     | 40      | 20120125    |
| Caelo    | Salicylic acid | 13344018         | 21760     | 40      | 20131020    |
| Euro OTC | Salicylic acid | 1509007          | 21906     | 40      | 20150929*   |
| Caelo    | Salicylic acid | 160109           | 22443     | 40      | 20160229*   |
| Fagron   | Salicylic acid | 16I15-B08-333932 | 23592     | 40      | 20170210    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Salicylic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 330 spectra of 9 reference samples from the substance/substance group *Salicylic acid*.

| Supplier | Substance      | Batch    | Sample ID          | Spectra |
|----------|----------------|----------|--------------------|---------|
| Caelo    | Salicylic acid | 82732219 | 20015              | 30      |
| Caelo    | Salicylic acid | 13344002 | 21436              | 60      |
| Caelo    | Salicylic acid | 13344018 | 21760 <sup>†</sup> | 20      |
| Euro OTC | Salicylic acid | 1509007  | 21906 <sup>†</sup> | 20      |
| Caelo    | Salicylic acid | 160109   | 22443 <sup>†</sup> | 20      |
| Caelo    | Salicylic acid | 160500   | 22448              | 60      |
| Euro OTC | Salicylic acid | 1605023  | 22685              | 40      |
| Caelo    | Salicylic acid | 171333   | 23277              | 40      |
| Euro OTC | Salicylic acid | 1707009  | 23556              | 40      |

- 146 399 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1123 spectra from 306 *Apo-Ident* customers from 265 batches from the substance/substance group *Salicylic acid*.

| Supplier                 | Substance      | Batch               | Spectra |
|--------------------------|----------------|---------------------|---------|
| Euro OTC                 | Salicylic acid | 1106014-01          | 1       |
| Caelo                    | Salicylic acid | 11197103            | 2       |
| Caelo                    | Salicylic acid | 12134720            | 8       |
| Gutenberg-Apotheke       | Salicylic acid | 12374208            | 1       |
| Caelo                    | Salicylic acid | 12374211            | 18      |
| Caelo                    | Salicylic acid | 12374212            | 2       |
| Caelo                    | Salicylic acid | 13344002            | 19      |
| Caelo                    | Salicylic acid | 13344013            | 10      |
| Caelo                    | Salicylic acid | 13344018            | 15      |
| Caelo                    | Salicylic acid | 13344020            | 15      |
| Euro OTC                 | Salicylic acid | 1406027-02          | 9       |
| Caelo                    | Salicylic acid | 14076202            | 3       |
| Caelo                    | Salicylic acid | 14076204            | 11      |
| Caelo                    | Salicylic acid | 14076207            | 10      |
| Caelo                    | Salicylic acid | 14300802            | 7       |
| Caelo                    | Salicylic acid | 14300809            | 10      |
| Caelo                    | Salicylic acid | 14336907            | 16      |
| Caelo                    | Salicylic acid | 14336911            | 15      |
| Caelo                    | Salicylic acid | 14336920            | 11      |
| Caelo                    | Salicylic acid | 15211809            | 10      |
| Caelo                    | Salicylic acid | 15217301            | 6       |
| Caelo                    | Salicylic acid | 15084403            | 5       |
| Anzag; 24.7.15; 15,82EUR | Salicylic acid | 15084402            | 1       |
| Caelo                    | Salicylic acid | 15211808            | 5       |
| Caelo                    | Salicylic acid | 15217302            | 14      |
| Caelo                    | Salicylic acid | 16010903            | 7       |
| Caelo                    | Salicylic acid | 16010907            | 4       |
| Caelo                    | Salicylic acid | 16010913            | 6       |
| Caelo                    | Salicylic acid | 16010917            | 4       |
| Caelo                    | Salicylic acid | 9220716             | 1       |
| Caelo                    | Salicylic acid | 11197117            | 2       |
| Caelo                    | Salicylic acid | 11311918            | 1       |
| Caelo                    | Salicylic acid | 11311923            | 3       |
| Anzag                    | Salicylic acid | 12036208            | 1       |
| Caelo                    | Salicylic acid | 12036216            | 5       |
| Caelo                    | Salicylic acid | 12036211            | 4       |
| Caelo                    | Salicylic acid | 12036225            | 4       |
| Caelo                    | Salicylic acid | 12134709            | 32      |
| Caelo                    | Salicylic acid | 12134710            | 3       |
| Caelo                    | Salicylic acid | 12134714            | 15      |
| Caelo                    | Salicylic acid | 12134717            | 12      |
| Sanacorp                 | Salicylic acid | 123036223           | 1       |
| Sanacorp                 | Salicylic acid | 12374205            | 1       |
| Caelo                    | Salicylic acid | 12374207-3454311172 | 1       |
| Caelo                    | Salicylic acid | 12H10-N08           | 5       |
| Euro OTC                 | Salicylic acid | 1303020-01          | 19      |
| Fagron                   | Salicylic acid | 13B14-N01           | 17      |
| Fagron                   | Salicylic acid | 13H01-N04           | 17      |
| Fagron                   | Salicylic acid | 13H01-N08           | 2       |
| Holdermann               | Salicylic acid | 14E26-B04294624     | 1       |
| Caelo                    | Salicylic acid | 3601413011-12374211 | 1       |
| Caelo                    | Salicylic acid | 12374207            | 9       |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------|------------------|----------------|
| 14076202                   | Salicylic acid   |                  | 1              |
| Caelo                      | Salicylic acid   | 7071403          | 1              |
| Caelo                      | Salicylic acid   | 10112014B        | 1              |
| Euro OTC                   | Salicylic acid   | 102455           | 1              |
| Caelo                      | Salicylic acid   | 10355907         | 1              |
| Euro OTC                   | Salicylic acid   | 1110020-01       | 4              |
| Alliance 19.12.12          | Salicylic acid   | 11311906         | 1              |
| Caelo                      | Salicylic acid   | 12036226         | 10             |
| Caelo                      | Salicylic acid   | 12134707         | 8              |
| Caelo                      | Salicylic acid   | 12134715         | 9              |
| Caelo                      | Salicylic acid   | 12134711         | 7              |
| Caesar & Loretz GmbH Hi... | Salicylic acid   | 12134714         | 1              |
| Caelo                      | Salicylic acid   | 12134719         | 3              |
| Caelo                      | Salicylic acid   | 12134721         | 1              |
| Caelo                      | Salicylic acid   | 12134722         | 4              |
| Klenk                      | Salicylic acid   | 12134722         | 1              |
| Caelo                      | Salicylic acid   | 12323403         | 3              |
| Caesar&Loretz GmbH/Anzag   | Salicylic acid   | 12374210         | 2              |
| Phönix                     | Salicylic acid   | 12374210         | 1              |
| Caelo                      | Salicylic acid   | 12374208         | 2              |
| Phönix                     | Salicylic acid   | 12374211         | 1              |
| Caelo                      | Salicylic acid   | 12374213         | 10             |
| Caelo                      | Salicylic acid   | 1274210          | 1              |
| Sanacorp                   | Salicylic acid   | 1303020-01       | 1              |
| Euro OTC                   | Salicylic acid   | 130302001        | 1              |
| Caelo                      | Salicylic acid   | 1303020-01       | 3              |
| EuRho                      | Salicylic acid   | 1303020-01       | 4              |
| Euro OTC                   | Salicylic acid   |                  | 1              |
| Euro OTC                   | Salicylic acid   | 1303020-02       | 4              |
| Caelo                      | Salicylic acid   | 13032014A        | 1              |
| Anzag/Henry Lamotte        | Salicylic acid   | 1334018          | 1              |
| Gehe                       | Salicylic acid   | 13344002         | 1              |
| AHD                        | Salicylic acid   | 13344002         | 1              |
| Caelo                      | Salicylic acid   | 13344003         | 10             |
| Caesar & Loretz GmbH       | Salicylic acid   | 13344003         | 1              |
| Fagron                     | Salicylic acid   | 13344013         | 1              |
| Caelo                      | Salicylic acid   | 13344014         | 5              |
| Sanacorp                   | Salicylic acid   | 13344014         | 1              |
| Caesar & Loretz GmbH Hi... | Salicylic acid   | 13344018         | 1              |
| Caelo                      | Salicylic acid   | 1334403          | 1              |
| Caelo                      | Salicylic acid   | 133454002        | 1              |
| AHD 22.07.14               | Salicylic acid   | 134002           | 1              |
| Fagron                     | Salicylic acid   | 13H01-N01        | 7              |
| Fagron                     | Salicylic acid   | 13H01N04         | 4              |
| Großhandel                 | Salicylic acid   | 13H01-N04        | 1              |
| Gehe                       | Salicylic acid   | 13H01-N04        | 1              |
| Caelo                      | Salicylic acid   | 13H01-N04        | 2              |
| Fagron                     | Salicylic acid   | 13H01N08         | 1              |
| Fagron                     | Salicylic acid   | 13K08-B31-290852 | 5              |
| Fagron                     | Salicylic acid   | 13K08-B31-290853 | 4              |
| Phönix                     | Salicylic acid   | 13K08-B31-290853 | 1              |
| Gehe                       | Salicylic acid   | 1406027-01       | 1              |
| Euro OTC                   | Salicylic acid   | 1406027-01       | 7              |
| Caelo                      | Salicylic acid   | 140602701        | 1              |
| Caelo                      | Salicylic acid   | 1406027-01       | 2              |
| EuRho                      | Salicylic acid   | 1406027-01       | 1              |
| Caelo                      | Salicylic acid   | 1406027-02       | 2              |
| Euro OTC                   | Salicylic acid   | 140602702        | 1              |
| EuRho                      | Salicylic acid   | 1406027-02       | 1              |
| Phönix Gotha               | Salicylic acid   | 14076201         | 1              |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------|------------------|----------------|
| Caelo                      | Salicylic acid   | 14076201         | 3              |
| Phoenix                    | Salicylic acid   | 14076201         | 1              |
| Euro OTC                   | Salicylic acid   | 1406027-02Mg1kg  | 1              |
| Caelo                      | Salicylic acid   | 14076203         | 8              |
| Caesar&Loretz GmbH/Anzag   | Salicylic acid   | 14076203         | 2              |
| Sanacorp 28.01.15 EK 12... | Salicylic acid   | 14076204         | 1              |
| Caelo                      | Salicylic acid   | 14076206         | 6              |
| Fagron                     | Salicylic acid   | 14076207         | 2              |
| Caelo                      | Salicylic acid   | 14076211         | 1              |
| Caelo                      | Salicylic acid   | 14300801         | 6              |
| Caelo                      | Salicylic acid   | 14076212         | 1              |
| Euro OTC                   | Salicylic acid   | 1408027          | 1              |
| Phönix Gotha               | Salicylic acid   | 14300801         | 1              |
| Caelo                      | Salicylic acid   | 14300804         | 5              |
| Caesar&Loretz Anzag        | Salicylic acid   | 14300804         | 2              |
| Caelo                      | Salicylic acid   | 14300805         | 8              |
| Phoenix goettingen         | Salicylic acid   | 14300808         | 1              |
| Caelo                      | Salicylic acid   | 14300806         | 1              |
| Caelo                      | Salicylic acid   | 14300808         | 1              |
| Caesar & Loretz GmbH       | Salicylic acid   | 14300809         | 1              |
| Caelo                      | Salicylic acid   | 14336904         | 1              |
| Caelo                      | Salicylic acid   | 1430802          | 1              |
| Caelo                      | Salicylic acid   | 14336905         | 7              |
| Caelo                      | Salicylic acid   | 14336906         | 1              |
| Noweda                     | Salicylic acid   | 14336907         | 2              |
| Caelo                      | Salicylic acid   | 14336908         | 1              |
| Caelo                      | Salicylic acid   | 14336912         | 6              |
| Fagron                     | Salicylic acid   | 14B05-B30        | 3              |
| Fagron                     | Salicylic acid   | 14B05B30         | 1              |
| Fagron                     | Salicylic acid   | 14B05-B30-290854 | 5              |
| Fagron                     | Salicylic acid   | 14E26B04         | 2              |
| Fagron                     | Salicylic acid   | 14E26-B04        | 7              |
| Fagron                     | Salicylic acid   | 14E26-B04294623  | 1              |
| Fagron                     | Salicylic acid   | 14E26-B04-294622 | 2              |
| Euro OTC                   | Salicylic acid   | 14E26-B04-294622 | 1              |
| Fagron                     | Salicylic acid   | 14E26-B04-294623 | 4              |
| Fagron                     | Salicylic acid   | 14E26B04294623   | 1              |
| Fagron                     | Salicylic acid   | 14E26-B04-294624 | 5              |
| Fagron                     | Salicylic acid   | 14L02-B02        | 5              |
| Fagron                     | Salicylic acid   | 14L02-B02-303557 | 10             |
| Fagron                     | Salicylic acid   | 14L02-B02-303558 | 6              |
| Fagron                     | Salicylic acid   | 14L02B02303557   | 1              |
| Caelo                      | Salicylic acid   | 15084401         | 3              |
| Novacyl, FR                | Salicylic acid   | 15084403         | 2              |
| Sanacorp                   | Salicylic acid   | 15084404         | 1              |
| Caelo                      | Salicylic acid   | 15084404         | 3              |
| Euro OTC                   | Salicylic acid   | 1509007-01       | 18             |
| Caelo                      | Salicylic acid   | 1509007-01       | 1              |
| Caelo                      | Salicylic acid   | 152117304        | 1              |
| Caelo                      | Salicylic acid   | 15211806         | 3              |
| Caesar&Loretz/AHD          | Salicylic acid   | 15211808         | 1              |
| Caelo                      | Salicylic acid   | 15211810         | 5              |
| Caesar&Loretz GmbH/Sana... | Salicylic acid   | 15217301         | 1              |
| Caelo                      | Salicylic acid   | 15217303         | 9              |
| Caelo                      | Salicylic acid   | 15217304         | 5              |
| Caelo                      | Salicylic acid   | 15217305         | 2              |
| Caelo                      | Salicylic acid   | 15217308         | 6              |
| Caelo                      | Salicylic acid   | 16010905         | 2              |
| Caelo                      | Salicylic acid   | 16010906         | 8              |
| Caelo                      | Salicylic acid   | 16050012         | 4              |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>        | <b>Spectra</b> |
|----------------------------|------------------|---------------------|----------------|
| Caelo                      | Salicylic acid   | 16072014A           | 1              |
| Caesar&Loretz GmbH,15.0... | Salicylic acid   | 16312001            | 1              |
| Caelo                      | Salicylic acid   | 1714Q1045           | 1              |
| Caelo                      | Salicylic acid   | 18121412            | 1              |
| Caelo                      | Salicylic acid   | 23071510            | 1              |
| Fagron                     | Salicylic acid   | 290852              | 1              |
| xxx                        | Salicylic acid   | 4311A-01045         | 1              |
| Sanacorp                   | Salicylic acid   | 68/AKD2             | 1              |
| Phönix                     | Salicylic acid   | 68/AKD4             | 1              |
| Farmalabor / Farmalabor    | Salicylic acid   | P1404195-002        | 1              |
| Caelo                      | Salicylic acid   |                     | 7              |
| Caelo                      | Salicylic acid   | 8170717             | 1              |
| Ichthyol/Noweda            | Salicylic acid   | 13344003            | 1              |
| Caaelo                     | Salicylic acid   | 14336911            | 1              |
| Caelo                      | Salicylic acid   | 14336913            | 1              |
| Caelo                      | Salicylic acid   | 14336919            | 6              |
| Sanacorp                   | Salicylic acid   | 14336919            | 1              |
| Lamotte/Sanacorp           | Salicylic acid   | 14E25-B04           | 1              |
| Caelo                      | Salicylic acid   | 15081601            | 1              |
| Euro OTC                   | Salicylic acid   | 1509007/02          | 1              |
| EurRho/ Anzag              | Salicylic acid   | 1509007-01          | 1              |
| Euro OTC                   | Salicylic acid   | 1509007-02          | 2              |
| EuRho 001                  | Salicylic acid   | 1509007-02          | 1              |
| Phönix                     | Salicylic acid   | 1509007-02          | 1              |
| Caelo                      | Salicylic acid   | 151224/1            | 1              |
| Caelo                      | Salicylic acid   | 15211807            | 2              |
| Phoenix                    | Salicylic acid   | 15211808            | 2              |
| Fagron                     | Salicylic acid   | 15211809            | 1              |
| Fagron                     | Salicylic acid   | 16/15-B08-330773    | 2              |
| Fagron                     | Salicylic acid   |                     | 1              |
| Ebert 24.08.16             | Salicylic acid   | 16010903            | 1              |
| Caelo                      | Salicylic acid   | 16010904            | 1              |
| Celo/ Sanacorp             | Salicylic acid   | 16010908            | 1              |
| Gehe                       | Salicylic acid   | 16010910            | 1              |
| Caelo                      | Salicylic acid   | 16010910            | 2              |
| Sana 04.02.17 Ek:13,83     | Salicylic acid   | 16010910            | 1              |
| Caelo                      | Salicylic acid   | 16010918            | 2              |
| Caelo                      | Salicylic acid   | 16010922            | 2              |
| Caelo                      | Salicylic acid   | 16010923            | 1              |
| Caelo                      | Salicylic acid   | 16050003            | 2              |
| Caelo                      | Salicylic acid   | 16010972            | 1              |
| Caelo                      | Salicylic acid   | 160500004           | 1              |
| Caelo                      | Salicylic acid   | 16050004            | 7              |
| Caelo                      | Salicylic acid   | 16050005            | 4              |
| Phönix                     | Salicylic acid   | 16050005            | 1              |
| Caelo                      | Salicylic acid   | 16050011            | 4              |
| Euro OTC                   | Salicylic acid   | 1605023/02          | 1              |
| Caelo                      | Salicylic acid   | 16050013            | 1              |
| Euro OTC                   | Salicylic acid   | 160502301           | 1              |
| Euro OTC                   | Salicylic acid   | 1605023-01          | 5              |
| Bombastus                  | Salicylic acid   | 1605023-01          | 1              |
| Caelo                      | Salicylic acid   | 16E02-B09-325355    | 1              |
| Euro OTC                   | Salicylic acid   | 1605023-02          | 1              |
| Fagron                     | Salicylic acid   | 16A18-B04-322905    | 2              |
| Fagron                     | Salicylic acid   | 16I15-B08-330773    | 1              |
| Euro OTC                   | Salicylic acid   | 1707009-01          | 1              |
| Caelo                      | Salicylic acid   | RAS1135100          | 1              |
| Caelo                      | Salicylic acid   | Validierungsmessung | 1              |
| Caelo                      | Salicylic acid   | 1101301             | 1              |
| Caelo                      | Salicylic acid   | 1738980             | 1              |

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| Supplier                   | Substance      | Batch        | Spectra |
|----------------------------|----------------|--------------|---------|
| Caelo                      | Salicylic acid | 8101204      | 1       |
| Caelo                      | Salicylic acid | 9112013A     | 1       |
| Caelo                      | Salicylic acid | 9091301      | 1       |
| Gehe 27.09.13              | Salicylic acid | 9220708      | 1       |
| Caesar&lorenz,Phoenix      | Salicylic acid | 9220710      | 1       |
| Caelo                      | Salicylic acid | 9220715      | 1       |
| Fagron                     | Salicylic acid | 102455-0002  | 2       |
| Caelo                      | Salicylic acid | 10291803     | 1       |
| GEHE                       | Salicylic acid | 102455-0002  | 1       |
| Caelo                      | Salicylic acid | 10291804     | 2       |
| Caelo                      | Salicylic acid | 10291808     | 1       |
| Caelo                      | Salicylic acid | 10291824     | 1       |
| Caelo                      | Salicylic acid | 10355911     | 3       |
| Caelo                      | Salicylic acid | 10355912     | 1       |
| Caesar & Loretz GmbH 40... | Salicylic acid | 10355916     | 1       |
| Caelo                      | Salicylic acid | 10355916     | 1       |
| Anzag                      | Salicylic acid | 1106014-01   | 1       |
| Gehe                       | Salicylic acid | 1106014-01   | 1       |
| Euro OTC                   | Salicylic acid | 1110020      | 1       |
| Noweda                     | Salicylic acid | 1110020-01   | 1       |
| Caesar&lorenz,Phoenix      | Salicylic acid | 11197104     | 1       |
| Spangropharm               | Salicylic acid | 11197104     | 1       |
| Caelo                      | Salicylic acid | 11197106     | 1       |
| Noweda                     | Salicylic acid | 11197105     | 1       |
| Caelo                      | Salicylic acid | 11197118     | 1       |
| Caelo                      | Salicylic acid | 11197121     | 1       |
| Fagron                     | Salicylic acid | 11197121     | 1       |
| Phönix, 02.11.2012         | Salicylic acid | 11197121     | 1       |
| VDL                        | Salicylic acid | 11197122     | 1       |
| Noweda                     | Salicylic acid | 11197123     | 2       |
| Caelo                      | Salicylic acid | 11197123     | 8       |
| Phönix                     | Salicylic acid | 11311902     | 1       |
| Noweda                     | Salicylic acid | 11311903     | 1       |
| Caelo                      | Salicylic acid | 11311902     | 1       |
| Caelo                      | Salicylic acid | 11311903     | 2       |
| Caelo                      | Salicylic acid | 11311904     | 2       |
| Caesar & Loretz GmbH D-... | Salicylic acid | 11311904     | 1       |
| Kehr                       | Salicylic acid | 11311904     | 1       |
| Gehe                       | Salicylic acid | 11311904     | 1       |
| Caelo                      | Salicylic acid | 11311905     | 1       |
| Caelo                      | Salicylic acid | 11311906     | 5       |
| Anzag am 08.06.2012        | Salicylic acid | 11311906     | 1       |
| Caelo                      | Salicylic acid | 11311910     | 2       |
| Caelo                      | Salicylic acid | 11311916     | 2       |
| Anzag 31.01.13 ek: 6,34EUR | Salicylic acid | 11311916     | 1       |
| Phönix                     | Salicylic acid | 11311917     | 1       |
| Ichthyol/Anzag             | Salicylic acid | 11311917     | 1       |
| Caelo                      | Salicylic acid | 11311917     | 4       |
| Caesar & Loretz GmbH, 4... | Salicylic acid | 11311917     | 1       |
| Caelo                      | Salicylic acid | 11311922     | 9       |
| Sanacorp                   | Salicylic acid | 11311922     | 1       |
| Anzag 05.01.13             | Salicylic acid | 11311922     | 1       |
| GEHE                       | Salicylic acid | 11311922     | 1       |
| Caesar & Loretz GmbH       | Salicylic acid | 11311922     | 1       |
| Ichthyol                   | Salicylic acid | 11311922     | 2       |
| Phönix 17.06.2013          | Salicylic acid | 11311923     | 1       |
| Caelo                      | Salicylic acid | 11311922     | 1       |
| Fagron                     | Salicylic acid | 11B14-N13    | 1       |
| Caelo                      | Salicylic acid | 1197106      | 1       |
| Euro OTC                   | Salicylic acid | 115465478596 | 1       |

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| <b>Supplier</b>          | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|--------------------------|------------------|--------------|----------------|
| Gehe                     | Salicylic acid   | 11D15-N08    | 1              |
| Fagron                   | Salicylic acid   | 11K10-N01    | 4              |
| Großhandel               | Salicylic acid   | 11K10-N01    | 1              |
| Fagron                   | Salicylic acid   | 11L19-N21    | 3              |
| Phönix                   | Salicylic acid   | 11127-N05    | 1              |
| Caelo                    | Salicylic acid   | 12036202     | 6              |
| Caelo                    | Salicylic acid   | 12036208     | 2              |
| Caelo                    | Salicylic acid   | 12036209     | 5              |
| Phönix Gotha             | Salicylic acid   | 12036210     | 1              |
| Noweda                   | Salicylic acid   | 12036210     | 1              |
| Caelo                    | Salicylic acid   | 12036210     | 3              |
| Caesar&lorenz,Anzag      | Salicylic acid   | 12036211     | 1              |
| Alliance Healthcare      | Salicylic acid   | 12036215     | 1              |
| Noweda                   | Salicylic acid   | 12036215     | 1              |
| Caelo                    | Salicylic acid   | 12036215     | 3              |
| Alliance Healthcare      | Salicylic acid   | 12036216     | 1              |
| Caelo                    | Salicylic acid   | 12036217     | 2              |
| Caelo                    | Salicylic acid   | 12036223     | 9              |
| Noweda                   | Salicylic acid   | 12036223     | 2              |
| Bombastus                | Salicylic acid   | 12036223     | 2              |
| Noweda                   | Salicylic acid   | 12036226     | 1              |
| Caelo                    | Salicylic acid   | 12036315     | 1              |
| EuRho                    | Salicylic acid   | 1206007-01   | 2              |
| Euro OTC                 | Salicylic acid   | 1206007-01   | 11             |
| Gehe                     | Salicylic acid   | 1206007-01   | 1              |
| Caelo                    | Salicylic acid   | 12104709     | 1              |
| Caelo                    | Salicylic acid   | 12134702     | 12             |
| Sanacorp                 | Salicylic acid   | 12134707     | 1              |
| AHD, 24.05.2013          | Salicylic acid   | 12134707     | 1              |
| Caelo                    | Salicylic acid   | 12134712     | 4              |
| Sanacorp                 | Salicylic acid   | 12134712     | 1              |
| Caelo                    | Salicylic acid   | 12134713     | 1              |
| carlo                    | Salicylic acid   | 12134714     | 2              |
| Sanacorp                 | Salicylic acid   | 12134715     | 1              |
| Caelo                    | Salicylic acid   | 12323401     | 2              |
| Caelo                    | Salicylic acid   | 123134712    | 1              |
| Phönix                   | Salicylic acid   | 12323401     | 1              |
| Caelo                    | Salicylic acid   | 12323402     | 2              |
| Bombastus                | Salicylic acid   | 12323403     | 1              |
| Caelo                    | Salicylic acid   | 1234         | 1              |
| Caelo                    | Salicylic acid   | 1234709      | 2              |
| Jenne                    | Salicylic acid   | 12345        | 1              |
| Caelo                    | Salicylic acid   | 12374204     | 1              |
| Caesar&Loretz GmbH/Anzag | Salicylic acid   | 12374204     | 1              |
| Caelo                    | Salicylic acid   | 12374205     | 14             |
| Europ Ots Pharma         | Salicylic acid   | 12374205     | 1              |
| Phönix Gotha             | Salicylic acid   | 12374207     | 1              |
| Caelo                    | Salicylic acid   | 12374210     | 3              |
| Fagron                   | Salicylic acid   | 12C20-N04    | 1              |
| Fagron                   | Salicylic acid   | 12C20-N12    | 6              |
| Großhandel               | Salicylic acid   | 12C20-N12    | 1              |
| Phönix                   | Salicylic acid   | 12C20-N12    | 1              |
| Fagron                   | Salicylic acid   | 12H10-N03    | 7              |
| Großhandel               | Salicylic acid   | 12H10-N03    | 1              |
| Fagron                   | Salicylic acid   | 12H10-N08    | 7              |
| Phoenix                  | Salicylic acid   | 12H10-No8    | 1              |
| Fagron                   | Salicylic acid   | 12H1-N03     | 1              |
| Phönix                   | Salicylic acid   | 1303020-01   | 1              |
| Eurho/Phoenix            | Salicylic acid   | 13B14-N01    | 2              |
| Gehe                     | Salicylic acid   | 13B14-N01    | 1              |

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| Supplier              | Substance      | Batch            | Spectra |
|-----------------------|----------------|------------------|---------|
| Caelo                 | Salicylic acid | 13B14-No1        | 2       |
| Caelo                 | Salicylic acid | 13H01-N01        | 1       |
| Fagron                | Salicylic acid | 13H01N01         | 1       |
| Caesar&lorenz,Phoenix | Salicylic acid | 14076212         | 1       |
| Euro OTC              | Salicylic acid | 14336920         | 1       |
| Fagron                | Salicylic acid | 14e26-b04-294623 | 1       |
| Caelo                 | Salicylic acid | 20111306         | 1       |
| Caelo                 | Salicylic acid | 1913Q-01045      | 1       |
| Caelo                 | Salicylic acid | 20151112-4       | 1       |
| Caelo                 | Salicylic acid | 20270312-2       | 1       |
| Caelo                 | Salicylic acid | 25041304         | 1       |
| Caelo                 | Salicylic acid | 3111J01045       | 1       |
| Fagron                | Salicylic acid | 3111Q-01045      | 1       |
| Caelo                 | Salicylic acid | 3613A-01045      | 1       |
| Caelo                 | Salicylic acid | 4010Q-01045      | 1       |
| Caelo                 | Salicylic acid | 7466             | 1       |
| Caelo                 | Salicylic acid | 82732109         | 1       |
| Caelo                 | Salicylic acid | A-100513-1       | 1       |
| Caelo                 | Salicylic acid | Ch12134702       | 1       |
| Fagron                | Salicylic acid | RAS1135100       | 1       |
| Fagron                | Salicylic acid | RAS1135300       | 1       |
| Fagron                | Salicylic acid | xxxxxxx          | 1       |

- 68 510 spectra from 414 *Apo-Ident* customers from a total of 23 540 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Salicylic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Salicylic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 330           | 0              | 146 399       |
| <b>Type C</b> | 0              | 1077          | 46             | 68 510        |

The substance/substance group *Salicylic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.1818 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 95.9038 % (> 95.6367 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20696     | 21906               | 4.28                         | 58.22                           |
| 21760     | 21906               | 1.57                         | 57.25                           |
| 21906     | 21906               | 0.00                         | 56.63                           |
| 22443     | 22443               | 0.00                         | 54.20                           |
| 23592     | 21906               | 2.81                         | 55.44                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Selenium yeast**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20906-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Selenium yeast

### Special notes

When selecting the *Selenium yeast* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Selenium yeast*:

| Supplier | Substance      | Batch       | Sample ID | Spectra | Certificate |
|----------|----------------|-------------|-----------|---------|-------------|
| Euro OTC | Selenium yeast | L1204012-01 | 20906     | 40      | 1403461     |
| Caelo    | Selenium yeast | 13347911    | 21377     | 40      | 1509355     |
| Caelo    | Selenium yeast | 17002202    | 23120     | 40      | 1707512     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Selenium yeast*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 3 reference samples from the substance/substance group *Selenium yeast*.

| Supplier | Substance      | Batch       | Sample ID | Spectra |
|----------|----------------|-------------|-----------|---------|
| Dr. Behr | Selenium yeast | P-07015253  | 20367     | 40      |
| Euro OTC | Selenium yeast | L1401013-01 | 21102     | 40      |
| Caelo    | Selenium yeast | 17002208    | 23446     | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 10 spectra from 4 *Apo-Ident* customers from 9 batches from the substance/substance group *Selenium yeast*.

| Supplier                   | Substance      | Batch    | Spectra |
|----------------------------|----------------|----------|---------|
| Caelo                      | Selenium yeast | 12165708 | 1       |
| Caesar & Loretz GmbH, 4... | Selenium yeast | 11318111 | 1       |
| Caelo                      | Selenium yeast | 13347906 | 1       |
| Caelo                      | Selenium yeast | 13347911 | 1       |
| Caelo                      | Selenium yeast | 15276208 | 1       |

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| Supplier | Substance      | Batch       | Spectra |
|----------|----------------|-------------|---------|
| Euro OTC | Selenium yeast | L1503040-01 | 2       |
| Euro OTC | Selenium yeast | L1210021-01 | 1       |
| Euro OTC | Selenium yeast | L1404004-01 | 1       |
| Euro OTC | Selenium yeast | L1401013-01 | 1       |

- 69 623 spectra from 414 *Apo-Ident* customers from a total of 23 792 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Selenium yeast* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Selenium yeast* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 80            | 40             | 146 509       |
| <b>Type C</b> | 0              | 8             | 2              | 69 617        |

The substance/substance group *Selenium yeast* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 66.6667 % (> 64.1667 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8817 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20906     | 20906               | 0.00                         | 34.56                           |
| 21377     | 21377               | 0.00                         | 36.62                           |
| 23120     | 23120               | 0.00                         | 28.36                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sildenafil citrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20852-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sildenafil citrate; Sildenafil citras

### Special notes

When selecting the *Sildenafil citrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sildenafil citrate*:

| Supplier | Substance          | Batch      | Sample ID | Spectra | Certificate |
|----------|--------------------|------------|-----------|---------|-------------|
| Fagron   | Sildenafil citrate | 13F24-N03  | 20852     | 40      | 1402052     |
| Fagron   | Sildenafil citrate | 13J15-N01  | 20927     | 80      | 20131030    |
| Euro OTC | Sildenafil citrate | 1311010-01 | 21621     | 40      | 20131209    |
| Caelo    | Sildenafil citrate | 160498     | 22446     | 40      | 20160307*   |
| Caelo    | Sildenafil citrate | 170715     | 23336     | 40      | 20170529*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 5 reference samples from the substance/substance group *Sildenafil citrate*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 4 reference samples from the substance/substance group *Sildenafil citrate*.

| Supplier | Substance          | Batch      | Sample ID          | Spectra |
|----------|--------------------|------------|--------------------|---------|
| Euro OTC | Sildenafil citrate | 1311010-01 | 21621 <sup>†</sup> | 20      |
| Caelo    | Sildenafil citrate | 160498     | 22446 <sup>†</sup> | 20      |
| Euro OTC | Sildenafil citrate | 1311010-04 | 23178              | 40      |
| Caelo    | Sildenafil citrate | 170715     | 23345              | 40      |

- 146 609 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 75 spectra from 28 *Apo-Ident* customers from 41 batches from the substance/substance group *Sildenafil citrate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier           | Substance          | Batch            | Spectra |
|--------------------|--------------------|------------------|---------|
| Caelo              | Sildenafil citrate | 2101403          | 1       |
| Euro OTC           | Sildenafil citrate | 13110-01         | 1       |
| Euro OTC           | Sildenafil citrate | 1311010-01       | 3       |
| Phönix/Polpharma   | Sildenafil citrate | 1311010-01       | 1       |
| Polpharma/Phoenix  | Sildenafil citrate | 131101001        | 1       |
| Gutenberg-Apotheke | Sildenafil citrate | 1311010-01       | 1       |
| Euro OTC           | Sildenafil citrate | 1311010-03       | 4       |
| Euro OTC           | Sildenafil citrate | 131101003        | 1       |
| Caelo              | Sildenafil citrate | 131101003        | 1       |
| Phoenix            | Sildenafil citrate | 1311010-04       | 2       |
| Euro OTC           | Sildenafil citrate | 131101004        | 1       |
| Euro OTC           | Sildenafil citrate | 1311010-04       | 1       |
| Euro OTC           | Sildenafil citrate | 1311010-05       | 1       |
| Fagron             | Sildenafil citrate | 13J15-N01        | 3       |
| Euro OTC           | Sildenafil citrate | 14051402         | 1       |
| Caelo              | Sildenafil citrate | 14074703         | 2       |
| Caelo              | Sildenafil citrate | 14074707         | 2       |
| Caelo              | Sildenafil citrate | 14074710         | 1       |
| Caelo              | Sildenafil citrate | 14074709         | 1       |
| Caelo              | Sildenafil citrate | 14074714         | 5       |
| Caelo              | Sildenafil citrate | 14074715         | 5       |
| Caelo              | Sildenafil citrate | 14074716         | 1       |
| Fagron             | Sildenafil citrate | 14A08-b04-290225 | 1       |
| Fagron             | Sildenafil citrate | 14H11-B01-303183 | 1       |
| Caelo              | Sildenafil citrate | 1407474          | 1       |
| Caelo              | Sildenafil citrate | 15097301         | 1       |
| Euro OTC           | Sildenafil citrate | 15097301         | 1       |
| Caelo              | Sildenafil citrate | 15097303         | 1       |
| Caelo              | Sildenafil citrate | 15097306         | 1       |
| Caelo              | Sildenafil citrate | 15097307         | 1       |
| Caelo              | Sildenafil citrate | 15097311         | 1       |
| Caelo              | Sildenafil citrate | 15097312         | 2       |
| Caelo              | Sildenafil citrate | 16049802         | 6       |
| Caelo              | Sildenafil citrate | 15F11-B02-314725 | 1       |
| Fagron             | Sildenafil citrate | 15f11-b02-320186 | 1       |
| Fagron             | Sildenafil citrate | 15F11-B02-320186 | 1       |
| Caelo              | Sildenafil citrate | 16049805         | 1       |
| Caelo              | Sildenafil citrate | 16049808         | 2       |
| Caelo              | Sildenafil citrate | 16049814         | 3       |
| Caelo              | Sildenafil citrate | 16049820         | 1       |
| Caelo              | Sildenafil citrate | 16049821         | 2       |
| Euro OTC           | Sildenafil citrate | 17081504         | 1       |
| Caelo              | Sildenafil citrate | 45097306         | 1       |
| Euro OTC           | Sildenafil citrate | 17061405         | 1       |
| Fagron             | Sildenafil citrate | 16F30-B02-324715 | 1       |
| Gehe               | Sildenafil citrate | 13F24-N03        | 1       |
| Caelo              | Sildenafil citrate | 1311010-01       | 1       |

- 69 558 spectra from 414 *Apo-Ident* customers from a total of 23 760 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sildenafil citrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all

relevant spectra of the various substances were compared with *Sildenafil citrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 240           | 0              | 71 146        |
| Type B | 0              | 120           | 0              | 146 609       |
| Type C | 0              | 75            | 0              | 69 558        |

The substance/substance group *Sildenafil citrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.0000 %) |
| Type C | 100.0000 % (> 99.8813 %) | 100.0000 % (> 92.0000 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20852     | 20852               | 0.00                         | 61.31                           |
| 20927     | 20852               | 5.10                         | 67.67                           |
| 21621     | 20852               | 11.60                        | 68.46                           |
| 22446     | 22446               | 0.00                         | 65.92                           |
| 23336     | 23336               | 0.00                         | 63.11                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Sodium acetate trihydrate</b>                                |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20984-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Sodium acetate trihydrate; Natrii acetas trihydricum; Natrii aceticum

### Special notes

When selecting the *Sodium acetate trihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sodium acetate trihydrate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Sodium acetate t... | 12316506 | 20984     | 40      | 1402111     |
| Caelo    | Sodium acetate t... | 13411404 | 21441     | 40      | 20140113    |
| Euro OTC | Sodium acetate t... | 1507020  | 21861     | 40      | 20150723*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Sodium acetate trihydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 6 reference samples from the substance/substance group *Sodium acetate trihydrate*.

| Supplier    | Substance                 | Batch    | Sample ID          | Spectra |
|-------------|---------------------------|----------|--------------------|---------|
| zu erfassen | Sodium acetate trihydrate | pending  | 20157              | 40      |
| Caelo       | Sodium acetate trihydrate | 13411404 | 21441 <sup>†</sup> | 20      |
| Euro OTC    | Sodium acetate trihydrate | 1507020  | 21861 <sup>†</sup> | 20      |
| Caelo       | Sodium acetate trihydrate | 163007   | 22760              | 40      |
| Euro OTC    | Sodium acetate trihydrate | 1608032  | 22802              | 40      |
| Euro OTC    | Sodium acetate trihydrate | 1706008  | 23547              | 40      |

- 146 529 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 32 spectra from 21 *Apo-Ident* customers from 16 batches from the substance/substance group *Sodium acetate trihydrate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier           | Substance                 | Batch     | Spectra |
|--------------------|---------------------------|-----------|---------|
| Caelo              | Sodium acetate trihydrate | 13295601  | 1       |
| Gehe               | Sodium acetate trihydrate | 13411412  | 3       |
| Caelo              | Sodium acetate trihydrate | 13411404  | 1       |
| Caelo              | Sodium acetate trihydrate | 13411418  | 2       |
| Caelo              | Sodium acetate trihydrate | 15118701  | 3       |
| Caelo              | Sodium acetate trihydrate | 151452009 | 1       |
| Caelo              | Sodium acetate trihydrate | 15145204  | 6       |
| Caelo              | Sodium acetate trihydrate | 15145209  | 2       |
| Ebert KKH 13.10.16 | Sodium acetate trihydrate | 15145204  | 1       |
| Caelo              | Sodium acetate trihydrate | 10353017  | 1       |
| Ebert KKH 13.10.16 | Sodium acetate trihydrate | 15145209  | 1       |
| Caelo              | Sodium acetate trihydrate | 12316506  | 1       |
| Caelo              | Sodium acetate trihydrate | 12027203  | 1       |
| Caelo              | Sodium acetate trihydrate | 12027202  | 3       |
| Phönix Gotha       | Sodium acetate trihydrate | 12316506  | 1       |
| Caelo              | Sodium acetate trihydrate | 12027228  | 1       |
| Caelo              | Sodium acetate trihydrate | 13295606  | 1       |
| Caelo              | Sodium acetate trihydrate | 12027211  | 1       |
| Caelo              | Sodium acetate trihydrate | 12027217  | 1       |

- 69 601 spectra from 414 *Apo-Ident* customers from a total of 23 785 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sodium acetate trihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sodium acetate trihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 180           | 20             | 146 529       |
| <b>Type C</b> | 0              | 31            | 1              | 69 601        |

The substance/substance group *Sodium acetate trihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 90.0000 % (> 88.5000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.9813 %) | 96.8750 % (> 87.5000 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.



### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20984     | 20984               | 0.00                         | 33.47                           |
| 21441     | 20984               | 2.78                         | 33.26                           |
| 21861     | 21861               | 0.00                         | 35.53                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sodium ascorbate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20520-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sodium ascorbate; Natrii ascorbas; Natrii ascorbinicum

### Special notes

When selecting the *Sodium ascorbate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sodium ascorbate*:

| Supplier | Substance        | Batch      | Sample ID | Spectra | Certificate |
|----------|------------------|------------|-----------|---------|-------------|
| Euro OTC | Sodium ascorbate | 1406018-01 | 21583     | 40      | 1411165     |
| Euro OTC | Sodium ascorbate | 1507030    | 21853     | 40      | 20150811*   |
| Euro OTC | Sodium ascorbate | 1506018    | 21865     | 40      | 20150706*   |
| Euro OTC | Sodium ascorbate | 1510017    | 21946     | 40      | 20151102*   |
| Euro OTC | Sodium ascorbate | 1601007    | 22304     | 40      | 20160120*   |
| Caelo    | Sodium ascorbate | 15429905   | 22899     | 40      | 20160118    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Sodium ascorbate*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 520 spectra of 15 reference samples from the substance/substance group *Sodium ascorbate*.

| Supplier | Substance        | Batch      | Sample ID          | Spectra |
|----------|------------------|------------|--------------------|---------|
| Euro OTC | Sodium ascorbate | 5061206    | 20520              | 40      |
| Euro OTC | Sodium ascorbate | 1406018-01 | 21583 <sup>†</sup> | 20      |
| Euro OTC | Sodium ascorbate | 1406018-01 | 21789              | 60      |
| Euro OTC | Sodium ascorbate | 1507030    | 21853 <sup>†</sup> | 20      |
| Euro OTC | Sodium ascorbate | 1506018    | 21865 <sup>†</sup> | 20      |
| Euro OTC | Sodium ascorbate | 1510017    | 21946 <sup>†</sup> | 20      |
| Euro OTC | Sodium ascorbate | 1601007    | 22304 <sup>†</sup> | 20      |
| Euro OTC | Sodium ascorbate | 1604001    | 22524              | 40      |
| Euro OTC | Sodium ascorbate | 1607044    | 22690              | 40      |
| Caelo    | Sodium ascorbate | 162857     | 22761              | 40      |
| Euro OTC | Sodium ascorbate | 1611015    | 22864              | 40      |
| Euro OTC | Sodium ascorbate | 1701054    | 23134              | 40      |
| Euro OTC | Sodium ascorbate | 1703012    | 23152              | 40      |
| Euro OTC | Sodium ascorbate | 1705013    | 23430              | 40      |
| Euro OTC | Sodium ascorbate | 1705014    | 23432              | 40      |

- 146 209 spectra from a total of 3180 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 19 spectra from 5 *Apo-Ident* customers from 18 batches from the substance/substance group *Sodium ascorbate*.

| Supplier | Substance        | Batch       | Spectra |
|----------|------------------|-------------|---------|
| Euro OTC | Sodium ascorbate | 1210026-01  | 1       |
| Euro OTC | Sodium ascorbate | L1308005-01 | 1       |
| Euro OTC | Sodium ascorbate | 13051406    | 1       |
| Euro OTC | Sodium ascorbate | 12061407    | 1       |
| Euro OTC | Sodium ascorbate | 11081401    | 1       |
| Caelo    | Sodium ascorbate | 14079404    | 1       |
| Euro OTC | Sodium ascorbate | 13031402    | 1       |
| Caelo    | Sodium ascorbate | 15180505    | 1       |
| Fagron   | Sodium ascorbate | L1308005-01 | 1       |
| Euro OTC | Sodium ascorbate | 4021401     | 1       |
| Euro OTC | Sodium ascorbate | 11121301    | 1       |
| Euro OTC | Sodium ascorbate | 16091301    | 1       |
| Euro OTC | Sodium ascorbate | 20091303    | 1       |
| Euro OTC | Sodium ascorbate | 7011405     | 1       |
| Caelo    | Sodium ascorbate | 27091302    | 1       |
| Fagron   | Sodium ascorbate | 12L27-N03   | 1       |
| Fagron   | Sodium ascorbate | 13C15-N01   | 1       |
| Euro OTC | Sodium ascorbate | 28081304    | 1       |
| Caelo    | Sodium ascorbate | L1210026-01 | 1       |

- 69 614 spectra from 414 *Apo-Ident* customers from a total of 23 783 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sodium ascorbate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sodium ascorbate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 240           | 0              | 71 146        |
| <b>Type B</b> | 0              | 517           | 3              | 146 209       |
| <b>Type C</b> | 0              | 19            | 0              | 69 614        |

The substance/substance group *Sodium ascorbate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.4231 % (> 98.8462 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21583            | 21583                      | 0.00                                | 71.03                                  |
| 21853            | 21853                      | 0.00                                | 63.52                                  |
| 21865            | 21865                      | 0.00                                | 58.79                                  |
| 21946            | 21946                      | 0.00                                | 65.66                                  |
| 22304            | 22304                      | 0.00                                | 53.21                                  |
| 22899            | 22304                      | 2.94                                | 53.11                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sodium benzoate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20479-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sodium benzoate; Natrii benzoas; Natrii benzoicum

### Special notes

When selecting the *Sodium benzoate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sodium benzoate*:

| Supplier | Substance       | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------------|------------|-----------|---------|-------------|
| Caelo    | Sodium benzoate | 11267016   | 20752     | 40      | 20110923    |
| Caelo    | Sodium benzoate | 13178619   | 21607     | 40      | 20130624    |
| Euro OTC | Sodium benzoate | 1409040-01 | 21713     | 40      | 20141021    |
| Euro OTC | Sodium benzoate | 1506019    | 21825     | 40      | 20150623*   |
| Euro OTC | Sodium benzoate | 1510044    | 22236     | 40      | 20151109*   |

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| Supplier | Substance       | Batch   | Sample ID | Spectra | Certificate |
|----------|-----------------|---------|-----------|---------|-------------|
| Euro OTC | Sodium benzoate | 1602020 | 22363     | 40      | 20160225*   |
| Euro OTC | Sodium benzoate | 1610037 | 22867     | 40      | 20161202*   |
| Euro OTC | Sodium benzoate | 1701045 | 22997     | 40      | 20170207*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 320 spectra of 8 reference samples from the substance/substance group *Sodium benzoate*. These samples are listed above in the [calibration samples](#) section.
- 71066 spectra from a total of 1544 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 400 spectra of 12 reference samples from the substance/substance group *Sodium benzoate*.

| Supplier | Substance       | Batch            | Sample ID          | Spectra |
|----------|-----------------|------------------|--------------------|---------|
| Caelo    | Sodium benzoate | 90834189         | 20191              | 40      |
| Fagron   | Sodium benzoate | 10A08-N04        | 20479              | 40      |
| Caelo    | Sodium benzoate | 13178619         | 21607 <sup>†</sup> | 20      |
| Euro OTC | Sodium benzoate | 1409040-01       | 21713 <sup>†</sup> | 20      |
| Euro OTC | Sodium benzoate | 1506019          | 21825 <sup>†</sup> | 20      |
| Euro OTC | Sodium benzoate | 1510044          | 22236 <sup>†</sup> | 20      |
| Euro OTC | Sodium benzoate | 1602020          | 22363 <sup>†</sup> | 20      |
| Caelo    | Sodium benzoate | 161371           | 22474              | 60      |
| Euro OTC | Sodium benzoate | 1607005          | 22670              | 40      |
| Fagron   | Sodium benzoate | 15B16-B07-308570 | 22895              | 40      |
| Caelo    | Sodium benzoate | 170558           | 23283              | 40      |
| Euro OTC | Sodium benzoate | 1707024          | 23613              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 329 spectra from a total of 3182 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 170 spectra from 113 *Apo-Ident* customers from 84 batches from the substance/substance group *Sodium benzoate*.

| Supplier         | Substance       | Batch            | Spectra |
|------------------|-----------------|------------------|---------|
| Caelo            | Sodium benzoate | 15044104         | 6       |
| Euro OTC         | Sodium benzoate | 1304024-01       | 5       |
| Euro OTC         | Sodium benzoate | 1506019-01       | 4       |
| Caelo            | Sodium benzoate | 15363424         | 3       |
| Euro OTC         | Sodium benzoate | 1510044-01       | 5       |
| Caelo            | Sodium benzoate | 15363409         | 2       |
| Caelo            | Sodium benzoate | 12158419         | 7       |
| Caelo            | Sodium benzoate | 11267013         | 1       |
| Caelo            | Sodium benzoate | 14166714         | 1       |
| Caelo            | Sodium benzoate | 11267016         | 1       |
| Fagron           | Sodium benzoate | 12H08-N06        | 2       |
| Fagron           | Sodium benzoate | 13/27-B03-288805 | 1       |
| Fagron           | Sodium benzoate | 13/27B03288805   | 1       |
| Euro OTC         | Sodium benzoate | 1307013-01       | 1       |
| Euro OTC         | Sodium benzoate | 1309027-01       | 2       |
| Caelo            | Sodium benzoate | 13178603         | 3       |
| EuroTOC / Noweda | Sodium benzoate | 130902701        | 1       |
| Caelo            | Sodium benzoate | 13178613         | 1       |
| Caelo            | Sodium benzoate | 13178619         | 2       |
| Caelo            | Sodium benzoate | 13178635         | 4       |
| Caelo            | Sodium benzoate | 13178647         | 2       |
| Fagron           | Sodium benzoate | 13H01-N02        | 1       |
| Caelo            | Sodium benzoate | 13178643         | 1       |
| Fagron           | Sodium benzoate | 13C14-N01        | 1       |
| Hedinger         | Sodium benzoate | 13I27-B03        | 1       |
| Fagron           | Sodium benzoate | 13I27-B03-288806 | 3       |
| Phoenix goettin  | Sodium benzoate | 13I27-B03-288806 | 1       |
| Fagron           | Sodium benzoate | 13J27-B03        | 1       |
| Fagron           | Sodium benzoate | 13127-B03-288806 | 1       |
| Fagron           | Sodium benzoate | 13127-Bo3-288805 | 1       |
| Euro OTC         | Sodium benzoate | 1404011-01       | 4       |
| Euro/ Phönix     | Sodium benzoate | 1404011-01       | 1       |
| Unisan           | Sodium benzoate | 1404011-01       | 1       |
| Euro OTC         | Sodium benzoate | 1409040-01       | 1       |
| Fagron           | Sodium benzoate | 1412             | 1       |
| Fagron           | Sodium benzoate | 14E12-B07        | 1       |
| Fagron           | Sodium benzoate | 14E12B07296717   | 1       |
| Fagron           | Sodium benzoate | 14E12Bo7296717   | 1       |
| Fagron           | Sodium benzoate | 14E12B07296717   | 1       |
| Caelo            | Sodium benzoate | 1503022-01       | 1       |
| Caelo            | Sodium benzoate | 15044102         | 5       |
| Phönix           | Sodium benzoate | 1510044/01       | 1       |
| Caelo            | Sodium benzoate | 15135001         | 6       |
| Caelo            | Sodium benzoate | 15363401         | 7       |

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| Supplier               | Substance       | Batch            | Spectra |
|------------------------|-----------------|------------------|---------|
| Caelo                  | Sodium benzoate | 15363402         | 1       |
| Hedinger/Phönix        | Sodium benzoate | 15363413         | 1       |
| Euro OTC               | Sodium benzoate | 1602020-01       | 2       |
| Fagron                 | Sodium benzoate | 15B16-B07-306571 | 2       |
| Fagron                 | Sodium benzoate | 1602020-01       | 1       |
| Euro OTC               | Sodium benzoate | 1607005-01       | 1       |
| Caelo                  | Sodium benzoate | 16137103         | 1       |
| Caelo                  | Sodium benzoate | 1610037-01       | 1       |
| Euro OTC               | Sodium benzoate | 1610037-01       | 1       |
| Caelo                  | Sodium benzoate | 16137112         | 1       |
| Caelo                  | Sodium benzoate | 16137118         | 1       |
| Caelo                  | Sodium benzoate | 16137113         | 1       |
| Caelo                  | Sodium benzoate | 24021501         | 1       |
| Caelo                  | Sodium benzoate | 2215Q-01891      | 1       |
| Euro OTC               | Sodium benzoate | 1112006-01       | 1       |
| Caelo                  | Sodium benzoate | kdfhdf           | 1       |
| Euro OTC               | Sodium benzoate | 1007019-01       | 1       |
| Caelo                  | Sodium benzoate | 4315A-01891      | 1       |
| EuRho                  | Sodium benzoate | 1112006-01       | 1       |
| Caelo                  | Sodium benzoate | 11267007         | 2       |
| Caelo                  | Sodium benzoate | 11346113         | 1       |
| Phönix 26.10.12        | Sodium benzoate | 1204011-01       | 2       |
| Caelo                  | Sodium benzoate | 1209018-0        | 1       |
| Euro OTC               | Sodium benzoate | 1209018-01       | 5       |
| Noweda                 | Sodium benzoate | 1209018-01       | 1       |
| Euro OTC               | Sodium benzoate | 1209018-18       | 1       |
| Caelo                  | Sodium benzoate | 12158401         | 1       |
| Anzag 19.11.2012       | Sodium benzoate | 12158402         | 1       |
| Caelo                  | Sodium benzoate | 12158414         | 1       |
| Caelo                  | Sodium benzoate | 12158418         | 1       |
| Caelo                  | Sodium benzoate | 12158424         | 1       |
| Caelo                  | Sodium benzoate | 12158439         | 3       |
| Fagron                 | Sodium benzoate | 12C05-N04        | 1       |
| Fagron                 | Sodium benzoate | 1250             | 1       |
| Fagron                 | Sodium benzoate | 12D02-N06        | 1       |
| Fagron                 | Sodium benzoate | 12G04-N04        | 1       |
| Phönix 04.03.2013      | Sodium benzoate | 12J23-N05        | 1       |
| Fagron                 | Sodium benzoate | 12J23-N05        | 3       |
| Phönix                 | Sodium benzoate | 12J23-N05        | 2       |
| Caelo                  | Sodium benzoate | 12J23-N05        | 1       |
| Fiebig 27.06.13 EK3,34 | Sodium benzoate | 1304024-01       | 1       |
| EuRho Anzag            | Sodium benzoate | 1304024-01       | 1       |
| Alliance Healthcare    | Sodium benzoate | 1304024-01       | 1       |
| Euro OTC               | Sodium benzoate | 130402401        | 2       |
| Caelo                  | Sodium benzoate | 13178605         | 3       |
| Fagron                 | Sodium benzoate | 13C14-N01        | 4       |
| Caelo                  | Sodium benzoate | 13178627         | 1       |
| Caelo                  | Sodium benzoate | 17061306         | 1       |
| Fagron                 | Sodium benzoate | 1913A-01981      | 1       |
| Fagron                 | Sodium benzoate | 24011401         | 1       |
| Euro OTC               | Sodium benzoate | 2604040V-05      | 1       |
| Caelo                  | Sodium benzoate | 5211I-01891      | 1       |
| Fagron                 | Sodium benzoate | test             | 1       |

- 69 463 spectra from 414 *Apo-Ident* customers from a total of 23 718 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#),



the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sodium benzoate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sodium benzoate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 320           | 0              | 71 066        |
| <b>Type B</b> | 0              | 395           | 5              | 146 329       |
| <b>Type C</b> | 0              | 170           | 0              | 69 463        |

The substance/substance group *Sodium benzoate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.1250 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 98.7500 % (> 98.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 96.4706 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20752     | 22363               | 7.28                         | 24.99                           |
| 21607     | 22363               | 5.48                         | 26.87                           |
| 21713     | 22236               | 6.78                         | 28.60                           |
| 21825     | 21825               | 0.00                         | 20.65                           |
| 22236     | 22236               | 0.00                         | 22.47                           |
| 22363     | 22363               | 0.00                         | 32.83                           |
| 22867     | 22867               | 0.00                         | 32.41                           |
| 22997     | 22997               | 0.00                         | 33.23                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das

alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sodium citrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20662-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sodium citrate; Natrii citras; Natrii citricum

### Special notes

When selecting the *Sodium citrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sodium citrate*:

| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate        |
|----------|----------------|------------------|-----------|---------|--------------------|
| Fagron   | Sodium citrate | 12E04-N05        | 20662     | 40      | 20120516           |
| Caelo    | Sodium citrate | 12045026         | 20918     | 40      | 20120307           |
| Caelo    | Sodium citrate | 13089335         | 21670     | 40      | AR-15-FG-000405-01 |
| Caelo    | Sodium citrate | 14112517         | 21718     | 40      | 20140416           |
| Fagron   | Sodium citrate | 14A13-B02-294541 | 21778     | 40      | 20140424           |

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| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate |
|----------|----------------|------------------|-----------|---------|-------------|
| Euro OTC | Sodium citrate | 1506041          | 21839     | 40      | 0000010492  |
| Euro OTC | Sodium citrate | 1511017          | 21997     | 40      | 20151130*   |
| Fagron   | Sodium citrate | 16F10-B01-326088 | 22843     | 40      | 20160711    |
| Euro OTC | Sodium citrate | 1610016          | 22859     | 40      | 20161102*   |
| Euro OTC | Sodium citrate | 1701029          | 22996     | 40      | 20170126*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 400 spectra of 10 reference samples from the substance/substance group *Sodium citrate*. These samples are listed above in the [calibration samples](#) section.
- 70 986 spectra from a total of 1542 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 340 spectra of 11 reference samples from the substance/substance group *Sodium citrate*.

| Supplier | Substance      | Batch            | Sample ID          | Spectra |
|----------|----------------|------------------|--------------------|---------|
| Euro OTC | Sodium citrate | 1205026-01       | 20652              | 40      |
| Caelo    | Sodium citrate | 12045008         | 20656              | 40      |
| Caelo    | Sodium citrate | 13089335         | 21670 <sup>†</sup> | 20      |
| Caelo    | Sodium citrate | 14112517         | 21718 <sup>†</sup> | 20      |
| Fagron   | Sodium citrate | 14A13-B02-294541 | 21778 <sup>†</sup> | 20      |
| Euro OTC | Sodium citrate | 1506041          | 21839 <sup>†</sup> | 20      |
| Euro OTC | Sodium citrate | 1511017          | 21997 <sup>†</sup> | 20      |
| Euro OTC | Sodium citrate | 1604030          | 22510              | 40      |
| Caelo    | Sodium citrate | 162179           | 22618              | 40      |
| Euro OTC | Sodium citrate | 1607040          | 22687              | 40      |
| Euro OTC | Sodium citrate | 1710006          | 23614              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 389 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 608 spectra from 254 *Apo-Ident* customers from 198 batches from the substance/substance group *Sodium citrate*.

| Supplier             | Substance      | Batch               | Spectra |
|----------------------|----------------|---------------------|---------|
| Caelo                | Sodium citrate | 13089317            | 9       |
| Euro OTC             | Sodium citrate | 1305001-01          | 13      |
| Caelo                | Sodium citrate | 14112518            | 3       |
| Fagron               | Sodium citrate | 13A07-N01           | 8       |
| Euro OTC             | Sodium citrate | 1311035-01          | 22      |
| Euro OTC             | Sodium citrate | 1412014-01          | 14      |
| VDL;16.05.15;3,83EUR | Sodium citrate | 14369406            | 1       |
| Caelo                | Sodium citrate | 14369407            | 27      |
| Caelo                | Sodium citrate | 14369406            | 2       |
| Caelo                | Sodium citrate | 14369408            | 1       |
| Caelo                | Sodium citrate | 14369423            | 6       |
| Caelo                | Sodium citrate | 14369413            | 10      |
| Caelo                | Sodium citrate | 16095702            | 1       |
| Caelo                | Sodium citrate | 11219012            | 5       |
| Caelo                | Sodium citrate | 11304311            | 5       |
| Euro OTC             | Sodium citrate | 1506041-01          | 15      |
| Euro OTC             | Sodium citrate | 1511017-01          | 14      |
| Caelo                | Sodium citrate | 12045008            | 5       |
| Caelo                | Sodium citrate | 12045011            | 7       |
| Fagron               | Sodium citrate | 13B28-N02           | 4       |
| Noweda               | Sodium citrate | 1205026-01          | 1       |
| Euro OTC             | Sodium citrate | 1211030-01          | 12      |
| Caelo                | Sodium citrate | 1234                | 3       |
| Caelo                | Sodium citrate | 13089335            | 8       |
| Fagron               | Sodium citrate | 13/24-B13-287921    | 4       |
| Fagron               | Sodium citrate | 13I24-B13-287921    | 2       |
| Caelo                | Sodium citrate | 14112502            | 17      |
| Caelo                | Sodium citrate | 12897               | 1       |
| Caelo                | Sodium citrate | 14112504            | 2       |
| Caelo                | Sodium citrate | 14112511            | 1       |
| Caelo                | Sodium citrate | 14112517            | 8       |
| Caelo                | Sodium citrate | 12045020            | 2       |
| Fagron               | Sodium citrate | 14A13b02300395      | 1       |
| Caelo                | Sodium citrate | 12045024            | 4       |
| Caelo                | Sodium citrate | 12045016-3451311172 | 1       |
| Caelo                | Sodium citrate | 12045026            | 9       |
| Caelo                | Sodium citrate | 13089309            | 4       |
| Sanacorp             | Sodium citrate | 13089308            | 1       |
| Caelo                | Sodium citrate | 13089306            | 1       |
| Caelo                | Sodium citrate | 13089313            | 3       |
| Herbasinica          | Sodium citrate |                     | 2       |
| Caelo                | Sodium citrate | 50815PMS01          | 1       |
| Euro OTC             | Sodium citrate |                     | 6       |
| Euro OTC             | Sodium citrate | 815757/6745         | 1       |

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| <b>Supplier</b>      | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------|------------------|------------------|----------------|
| Fagron               | Sodium citrate   | 815Q-01900       | 1              |
| Caelo                | Sodium citrate   | 1042             | 1              |
| Gatt-Koller          | Sodium citrate   | 1073/04121412    | 1              |
| Caelo                | Sodium citrate   | 11081514         | 1              |
| Caelo                | Sodium citrate   | 1107011-02       | 2              |
| Caelo                | Sodium citrate   | 1123588946       | 1              |
| Caelo                | Sodium citrate   | 1112517          | 1              |
| Caelo                | Sodium citrate   | 1151351          | 2              |
| Fagron               | Sodium citrate   | 1161207          | 3              |
| Caelo                | Sodium citrate   | 1161207          | 2              |
| Caesar/Noweda        | Sodium citrate   | 12045008         | 2              |
| Fagron               | Sodium citrate   | 1172108          | 1              |
| Fagron               | Sodium citrate   | 1176767          | 2              |
| Euro OTC             | Sodium citrate   | 1205026-02       | 4              |
| Caelo                | Sodium citrate   | 1234Test         | 1              |
| Caelo                | Sodium citrate   | 123456789        | 1              |
| Euro OTC             | Sodium citrate   | 12345            | 2              |
| Caelo                | Sodium citrate   | 123456           | 1              |
| Caelo                | Sodium citrate   | 123658           | 1              |
| Caelo                | Sodium citrate   | 123Test          | 3              |
| Caelo                | Sodium citrate   | 125874566        | 1              |
| Caelo                | Sodium citrate   | 123test          | 2              |
| Caelo                | Sodium citrate   | 1256825          | 1              |
| Caelo                | Sodium citrate   | 128896           | 1              |
| Fagron               | Sodium citrate   | 12J26-N02        | 3              |
| Fargon/Alliance HC   | Sodium citrate   | 13/24-B13-287921 | 1              |
| Caelo                | Sodium citrate   | 13/24-B13-287921 | 1              |
| Caelo                | Sodium citrate   | 13089305         | 1              |
| Caelo                | Sodium citrate   | 13089308         | 8              |
| Caelo                | Sodium citrate   | 13089314         | 1              |
| Caelo                | Sodium citrate   | 13089318         | 1              |
| Caelo                | Sodium citrate   | 13089319         | 4              |
| Caelo                | Sodium citrate   | 13089325         | 3              |
| Caelo                | Sodium citrate   | 13089331         | 9              |
| Caelo                | Sodium citrate   | 13089326         | 1              |
| Sanacorp             | Sodium citrate   | 13089331         | 1              |
| Bombastus            | Sodium citrate   | 13089334         | 1              |
| Caesar & Loretz GmbH | Sodium citrate   | 13089334         | 1              |
| Caelo                | Sodium citrate   | 131103501        | 1              |
| Sanacorp             | Sodium citrate   | 1311035-01       | 1              |
| Gehe                 | Sodium citrate   | 1311035-01       | 1              |
| Caelo                | Sodium citrate   | 1389318          | 1              |
| Fagron               | Sodium citrate   | 13A07-N01        | 1              |
| Caelo                | Sodium citrate   | 13B28-N02        | 3              |
| Fagron               | Sodium citrate   | 13D09-N01        | 4              |
| Fagron               | Sodium citrate   | 13E27-N12        | 1              |
| Euro OTC             | Sodium citrate   | 13I24-B13-287921 | 1              |
| Euro OTC             | Sodium citrate   | 1404033-01       | 12             |
| Caelo                | Sodium citrate   | 1404033-01       | 3              |
| Euro OTC             | Sodium citrate   | 140403301        | 5              |
| Gehe/Euro            | Sodium citrate   | 1404033-01       | 2              |
| Caelo                | Sodium citrate   | 140510/1         | 1              |
| Euro OTC             | Sodium citrate   | 14112014-01      | 1              |
| Caesar&Loretz GmbH   | Sodium citrate   | 14112502         | 1              |
| Fagron               | Sodium citrate   | 14112502         | 1              |
| Caesar & Loretz GmbH | Sodium citrate   | 14112517         | 1              |
| Caelo                | Sodium citrate   | 14112520         | 1              |
| Caelo                | Sodium citrate   | 1411502          | 1              |
| Gehe/Euro            | Sodium citrate   | 1412014-01       | 6              |
| EuRho                | Sodium citrate   | 1412014-01       | 1              |

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| <b>Supplier</b>          | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|--------------------------|------------------|-------------------|----------------|
| Fagron                   | Sodium citrate   | 1412014-01        | 1              |
| Caelo                    | Sodium citrate   | 14369402          | 3              |
| Euro OTC                 | Sodium citrate   | 14201401          | 1              |
| Sanacorp                 | Sodium citrate   | 1436407           | 1              |
| Caesar & Loretz GmbH     | Sodium citrate   | 14369406          | 1              |
| Caesar&Loretz GmbH/Anzag | Sodium citrate   | 14369407          | 1              |
| Caelo                    | Sodium citrate   | 14369411          | 3              |
| Caelo                    | Sodium citrate   | 14369414          | 1              |
| Caelo                    | Sodium citrate   | 14369415          | 1              |
| Phoenix 30.05.2016       | Sodium citrate   | 14369423          | 1              |
| Caelo                    | Sodium citrate   | 14369424          | 2              |
| Fagron                   | Sodium citrate   | 14A13-B02-294541  | 4              |
| Fagron                   | Sodium citrate   | 14A13-B02         | 1              |
| Fagron                   | Sodium citrate   | 14A13-B02-300395  | 3              |
| Caelo                    | Sodium citrate   | 14838             | 1              |
| Phoenix                  | Sodium citrate   | 1506041-01        | 2              |
| Caelo                    | Sodium citrate   | 1506041-01        | 1              |
| Euro OTC                 | Sodium citrate   | 151101701         | 1              |
| Caelo                    | Sodium citrate   | 1511017-01        | 3              |
| Phoenix                  | Sodium citrate   | 1511017-01        | 2              |
| Fagron                   | Sodium citrate   | 1511017-01        | 2              |
| Caelo                    | Sodium citrate   | 15212705          | 1              |
| Euro OTC                 | Sodium citrate   | 15111017-01       | 1              |
| Caelo                    | Sodium citrate   | 154662            | 1              |
| Euro OTC                 | Sodium citrate   | 16070-01          | 1              |
| Euro OTC                 | Sodium citrate   | 156422            | 1              |
| Fagron                   | Sodium citrate   | 15C27-B01-309893  | 1              |
| Euro OTC                 | Sodium citrate   | 160740-01         | 1              |
| Fagron                   | Sodium citrate   | 15C27-B01-3211097 | 1              |
| Euro OTC                 | Sodium citrate   | 1607040-01        | 4              |
| Caelo                    | Sodium citrate   | 1607040-01        | 1              |
| Eurho/ Noweda            | Sodium citrate   | 1607040-01        | 1              |
| EuRho                    | Sodium citrate   | 1607040-01        | 1              |
| Caelo                    | Sodium citrate   | 16095707          | 1              |
| Euro OTC                 | Sodium citrate   | 1610016-01        | 10             |
| Caelo                    | Sodium citrate   | 16217905          | 4              |
| Caelo                    | Sodium citrate   | 16217902          | 1              |
| Euro OTC                 | Sodium citrate   | 1701029-01        | 3              |
| Euro OTC                 | Sodium citrate   | 1645265           | 3              |
| Euro OTC                 | Sodium citrate   | 17061407          | 1              |
| Fagron                   | Sodium citrate   | 16F10-B01-326088  | 1              |
| Caelo                    | Sodium citrate   | 17081501          | 1              |
| Fagron                   | Sodium citrate   | 17A26-B04         | 1              |
| Euro OTC                 | Sodium citrate   | 23062015C         | 1              |
| Euro OTC                 | Sodium citrate   | 2114M1900         | 1              |
| Caelo                    | Sodium citrate   | 2413A-01900       | 1              |
| Caelo                    | Sodium citrate   | 220914PML01       | 1              |
| Caelo                    | Sodium citrate   | 2345678           | 1              |
| Euro OTC                 | Sodium citrate   | 25425             | 2              |
| Euro OTC                 | Sodium citrate   | 2546426           | 1              |
| Euro OTC                 | Sodium citrate   | 3032805           | 2              |
| Euro OTC                 | Sodium citrate   | 3454              | 1              |
| Caelo                    | Sodium citrate   | 2815A-01900       | 1              |
| Euro OTC                 | Sodium citrate   | 358528            | 1              |
| Caelo                    | Sodium citrate   | 459842            | 1              |
| Bombastus                | Sodium citrate   | 73155098          | 1              |
| Euro OTC                 | Sodium citrate   | 345678            | 1              |
| sanacorp                 | Sodium citrate   | 9/AKD12           | 1              |
| Aug. Hedinger            | Sodium citrate   | 8765456           | 1              |
| Caelo                    | Sodium citrate   | Test              | 1              |

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| Supplier            | Substance      | Batch              | Spectra |
|---------------------|----------------|--------------------|---------|
| Caelo               | Sodium citrate |                    | 8       |
| Fagron              | Sodium citrate | 712A-01900         | 1       |
| Euro OTC            | Sodium citrate | 1004010-01         | 1       |
| Caelo               | Sodium citrate | 713A-01900         | 1       |
| Caelo               | Sodium citrate | 70214PJK01         | 1       |
| Caelo               | Sodium citrate | TestmessungnachRep | 1       |
| Euro OTC            | Sodium citrate | 1073240            | 1       |
| Euro OTC            | Sodium citrate | 1107011-01         | 1       |
| anzag,12.12.12      | Sodium citrate | 1049088            | 1       |
| EuRho               | Sodium citrate | 1107011-02         | 1       |
| Euro OTC            | Sodium citrate | 1107011-02         | 1       |
| Caelo               | Sodium citrate | 11121303           | 1       |
| EuRho/Sanacorp      | Sodium citrate | 1107011-02         | 1       |
| Noweda              | Sodium citrate | 11127001           | 1       |
| Caelo               | Sodium citrate | 1111111            | 1       |
| Caelo               | Sodium citrate | 11304305           | 1       |
| Caelo               | Sodium citrate | 11304312           | 2       |
| Caelo               | Sodium citrate | 12045001           | 2       |
| Caelo               | Sodium citrate | 12045002           | 1       |
| Caelo               | Sodium citrate | 12045004           | 3       |
| Phönix 19.12.2012   | Sodium citrate | 12/10-N01          | 1       |
| Fagron              | Sodium citrate | 11L05-N01          | 1       |
| Test                | Sodium citrate |                    | 1       |
| Caelo               | Sodium citrate | 12045005           | 3       |
| Noweda              | Sodium citrate | 12045004           | 1       |
| Caelo               | Sodium citrate | 12045007           | 1       |
| Caelo               | Sodium citrate | 12045006           | 1       |
| Caelo               | Sodium citrate | 12045012           | 2       |
| Caelo               | Sodium citrate | 12045016           | 5       |
| Caelo               | Sodium citrate | 12045017           | 2       |
| Caelo               | Sodium citrate | 12045019           | 6       |
| Erika apotheke      | Sodium citrate | 12045020           | 1       |
| Caelo               | Sodium citrate | 12045021           | 1       |
| Noweda              | Sodium citrate | 12045026           | 1       |
| Phönix/EuRho        | Sodium citrate | 1205026-02         | 1       |
| Anzag               | Sodium citrate | 1205026-02         | 1       |
| EuRho               | Sodium citrate | 1205026-02         | 1       |
| Phönix              | Sodium citrate | 1205026-02         | 1       |
| Gehe                | Sodium citrate | 1211030-01         | 1       |
| Phönix              | Sodium citrate | 1211030-01         | 3       |
| Alliance Healthcare | Sodium citrate | 1211030-01         | 1       |
| Caelo               | Sodium citrate | 121103001          | 1       |
| Test                | Sodium citrate | 1234               | 1       |
| Fagron              | Sodium citrate | 12339502           | 1       |
| Fagron              | Sodium citrate | 1234567            | 1       |
| Fagron              | Sodium citrate | 12A05-N04          | 4       |
| Caelo               | Sodium citrate | 12345678           | 1       |
| Fagron              | Sodium citrate | 12I10-N01          | 2       |
| Fagron              | Sodium citrate | 12E04-N05          | 2       |
| anzag, 14.12.2012   | Sodium citrate | 12I10-N06          | 1       |
| Euro/Phönix         | Sodium citrate | 1305001-01         | 1       |
| Caelo               | Sodium citrate | 13089304           | 3       |
| Caelo               | Sodium citrate | 1308908            | 1       |
| Europ Ots Pharma    | Sodium citrate | 13089304           | 1       |
| Caelo               | Sodium citrate | 13089329           | 1       |
| Euro OTC            | Sodium citrate | 1311025-01         | 1       |
| Euro OTC            | Sodium citrate | 1413M-01900        | 1       |
| Caelo               | Sodium citrate | 21121203           | 1       |
| Euro OTC            | Sodium citrate | 1521017-01         | 1       |
| Euro OTC            | Sodium citrate | 20200810-6         | 1       |

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| Supplier     | Substance      | Batch              | Spectra |
|--------------|----------------|--------------------|---------|
| Euro OTC     | Sodium citrate | 22101305           | 1       |
| Caelo        | Sodium citrate | 25383143           | 1       |
| Fagron       | Sodium citrate | 24121301           | 1       |
| Euro OTC     | Sodium citrate | 30111301           | 1       |
| Caelo        | Sodium citrate | 22131-01900        | 1       |
| Euro OTC     | Sodium citrate | 2903001-01         | 1       |
| Fagron       | Sodium citrate | 31051202           | 1       |
| fragon       | Sodium citrate |                    | 1       |
| Fagron       | Sodium citrate | 3311E-01900        | 1       |
| Caelo        | Sodium citrate | 4351235            | 1       |
| Caelo        | Sodium citrate | 4111Q-01900        | 1       |
| EuRho        | Sodium citrate | 4611M-01900        | 1       |
| Phönix Gotha | Sodium citrate | 52666276           | 1       |
| Caelo        | Sodium citrate | 49131-01900        | 1       |
| Caelo        | Sodium citrate | 8/AKD41            | 1       |
| Caelo        | Sodium citrate | K-280313-1         | 1       |
| Fagron       | Sodium citrate | Probe              | 1       |
| HiperScan    | Sodium citrate |                    | 1       |
| Unisan       | Sodium citrate | S/WReferenzUmstell | 1       |
| Fagron       | Sodium citrate | 14A13-B02-3003955  | 1       |
| Fagron       | Sodium citrate | 15C27-B01-316106   | 1       |
| Fagron       | Sodium citrate | 15C27-B01-312231   | 1       |
| Fagron       | Sodium citrate | 15C27-B01-321097   | 1       |
| Caelo        | Sodium citrate | 15C27-B01-309893   | 1       |
| Fagron       | Sodium citrate | 16F10-B01-327510   | 1       |
| Phönix       | Sodium citrate | 12045024           | 1       |
| Großhandel   | Sodium citrate | 12045026           | 1       |
| Caelo        | Sodium citrate | 1204521            | 1       |

- 69 025 spectra from 414 *Apo-Ident* customers from a total of 23 613 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sodium citrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sodium citrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 400           | 0              | 70 986        |
| <b>Type B</b> | 0              | 340           | 0              | 146 389       |
| <b>Type C</b> | 0              | 606           | 2              | 69 025        |

The substance/substance group *Sodium citrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.2353 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 99.6711 % (> 99.1776 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20662     | 21839               | 3.81                         | 41.79                           |
| 20918     | 21670               | 5.29                         | 41.69                           |
| 21670     | 21670               | 0.00                         | 41.08                           |
| 21718     | 21670               | 3.14                         | 41.31                           |
| 21778     | 21670               | 3.22                         | 41.52                           |
| 21839     | 21839               | 0.00                         | 42.09                           |
| 21997     | 21997               | 0.00                         | 42.40                           |
| 22843     | 21839               | 5.38                         | 42.67                           |
| 22859     | 22859               | 0.00                         | 36.25                           |
| 22996     | 22996               | 0.00                         | 40.95                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sodium cromoglicate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20775-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sodium cromoglicate; Natrii cromoglicas; Natrii cromoglicinum

### Special notes

When selecting the *Sodium cromoglicate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sodium cromoglicate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Fagron   | Sodium cromoglic... | 12C09-N02  | 20775     | 79      | 1401553     |
| Caelo    | Sodium cromoglic... | 11114501   | 20776     | 80      | 20110518    |
| Fagron   | Sodium cromoglic... | 13G24-N04  | 21260     | 40      | 20130515    |
| Caelo    | Sodium cromoglic... | 13232802   | 21375     | 20      | 1505352     |
| Euro OTC | Sodium cromoglic... | 1403017-01 | 21981     | 40      | 20140505    |

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| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Sodium cromoglic... | 15224404 | 21990     | 40      | 20150625    |
| Euro OTC | Sodium cromoglic... | 1510018  | 22231     | 40      | 20151109*   |
| Euro OTC | Sodium cromoglic... | 1703027  | 23383     | 40      | 20170405*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 379 spectra of 8 reference samples from the substance/substance group *Sodium cromoglicate*. These samples are listed above in the [calibration samples](#) section.
- 71 007 spectra from a total of 1544 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 500 spectra of 11 reference samples from the substance/substance group *Sodium cromoglicate*.

| Supplier | Substance           | Batch            | Sample ID          | Spectra |
|----------|---------------------|------------------|--------------------|---------|
| Caelo    | Sodium cromoglicate | 11114502         | 20289              | 40      |
| Euro OTC | Sodium cromoglicate | 1112003-01       | 20778              | 40      |
| Caelo    | Sodium cromoglicate | 13232802         | 21376              | 100     |
| Euro OTC | Sodium cromoglicate | 1403017-01       | 21981 <sup>†</sup> | 20      |
| Caelo    | Sodium cromoglicate | 15224404         | 21990 <sup>†</sup> | 20      |
| Euro OTC | Sodium cromoglicate | 1510018          | 22231 <sup>†</sup> | 20      |
| Fagron   | Sodium cromoglicate | 15C23-B01-307751 | 22972              | 40      |
| Euro OTC | Sodium cromoglicate | 1403017-01       | 21981SI            | 60      |
| Caelo    | Sodium cromoglicate | 15224404         | 21990SI            | 60      |
| Euro OTC | Sodium cromoglicate | 1510018          | 22231SI            | 60      |
| Fagron   | Sodium cromoglicate | 15C23-B01-307751 | 22972SI            | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 229 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 9 spectra from 7 *Apo-Ident* customers from 8 batches from the substance/substance group *Sodium cromoglicate*.

| Supplier | Substance           | Batch       | Spectra |
|----------|---------------------|-------------|---------|
| Fagron   | Sodium cromoglicate | 13G24-N04   | 1       |
| Caelo    | Sodium cromoglicate | 5113A-02831 | 1       |
| Fagron   | Sodium cromoglicate | 12D26-N12   | 1       |
| Fagron   | Sodium cromoglicate | 13E22-N11   | 1       |
| Caelo    | Sodium cromoglicate | 15224404    | 1       |
| Euro OTC | Sodium cromoglicate | 1403017-01  | 1       |
| Caelo    | Sodium cromoglicate | 12301101    | 2       |
| Caelo    | Sodium cromoglicate | 12301102    | 1       |

- 69 624 spectra from 414 *Apo-Ident* customers from a total of 23 793 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sodium cromoglicate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sodium cromoglicate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 378           | 1              | 71 007        |
| <b>Type B</b> | 0              | 463           | 37             | 146 229       |
| <b>Type C</b> | 0              | 8             | 1              | 69 624        |

The substance/substance group *Sodium cromoglicate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate        |
|---------------|--------------------------|-------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 99.7361 % (> 98.9446 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 92.6000 % (> 92.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)               |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several

new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20775     | 20775               | 0.00                         | 64.07                           |
| 20776     | 22231               | 19.45                        | 68.66                           |
| 21260     | 22231               | 7.39                         | 63.57                           |
| 21375     | 21375               | 0.00                         | 54.76                           |
| 21981     | 22231               | 18.69                        | 64.23                           |
| 21990     | 22231               | 17.24                        | 65.58                           |
| 22231     | 22231               | 0.00                         | 64.23                           |
| 23383     | 23383               | 0.00                         | 60.87                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sodium cyclamate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20917-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sodium cyclamate; Natrii cyclamas; Natrii cyclamicum

### Special notes

When selecting the *Sodium cyclamate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sodium cyclamate*:

| Supplier | Substance        | Batch    | Sample ID | Spectra | Certificate |
|----------|------------------|----------|-----------|---------|-------------|
| Caelo    | Sodium cyclamate | 12256803 | 20917     | 40      | 1401418     |
| Caelo    | Sodium cyclamate | 12105622 | 21380     | 40      | 20120423    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Sodium cyclamate*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 2 reference samples from the substance/substance group *Sodium cyclamate*.

| Supplier | Substance        | Batch    | Sample ID | Spectra |
|----------|------------------|----------|-----------|---------|
| Caelo    | Sodium cyclamate | 9350509  | 20137     | 60      |
| Caelo    | Sodium cyclamate | 16119302 | 23259     | 40      |

- 146 629 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 17 spectra from 12 *Apo-Ident* customers from 12 batches from the substance/substance group *Sodium cyclamate*.

| Supplier | Substance        | Batch    | Spectra |
|----------|------------------|----------|---------|
| Caelo    | Sodium cyclamate | 13359807 | 1       |
| Caelo    | Sodium cyclamate | 12105618 | 2       |
| Caelo    | Sodium cyclamate | 12105613 | 1       |
| Caelo    | Sodium cyclamate | 12256807 | 1       |
| Caelo    | Sodium cyclamate | 12105622 | 1       |
| Caelo    | Sodium cyclamate | 15201601 | 2       |

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| Supplier             | Substance        | Batch        | Spectra |
|----------------------|------------------|--------------|---------|
| Caesar & Loretz GmbH | Sodium cyclamate | 12105622     | 1       |
| Caelo                | Sodium cyclamate | 15201606     | 1       |
| Caelo                | Sodium cyclamate | 16119302     | 1       |
| Phoenix              | Sodium cyclamate | 787/03100611 | 1       |
| Caelo                | Sodium cyclamate | 10380915     | 2       |
| anzag,13.12.12       | Sodium cyclamate | 12256803     | 1       |
| Caelo                | Sodium cyclamate | 11204205     | 1       |
| Caelo                | Sodium cyclamate | 12256803     | 1       |

- 69616 spectra from 414 *Apo-Ident* customers from a total of 23 789 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sodium cyclamate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sodium cyclamate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 90            | 10             | 146 629       |
| <b>Type C</b> | 0              | 15            | 2              | 69 616        |

The substance/substance group *Sodium cyclamate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 90.0000 % (> 87.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20917     | 20917               | 0.00                         | 80.63                           |
| 21380     | 20917               | 13.20                        | 80.94                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sodium edetate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20937-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sodium edetate; Dinatrii edetas; Natrii aethylendiaminum tetraaceticum

### Special notes

When selecting the *Sodium edetate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sodium edetate*:

| Supplier | Substance      | Batch            | Sample ID | Spectra | Certificate |
|----------|----------------|------------------|-----------|---------|-------------|
| Fagron   | Sodium edetate | 13E15-N05        | 20937     | 40      | 1402193     |
| Caelo    | Sodium edetate | 13142009         | 21362     | 40      | 20130524    |
| Caelo    | Sodium edetate | 161364           | 22465     | 40      | 20160504*   |
| Euro OTC | Sodium edetate | 1609023          | 22915     | 40      | 20170106*   |
| Fagron   | Sodium edetate | 16F21-B02-325085 | 22926     | 40      | 20160713    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Sodium edetate*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 193 spectra of 6 reference samples from the substance/substance group *Sodium edetate*.

| Supplier | Substance      | Batch      | Sample ID          | Spectra |
|----------|----------------|------------|--------------------|---------|
| Fagron   | Sodium edetate | 10C10-N04  | 20190              | 40      |
| Caelo    | Sodium edetate | 161364     | 22465 <sup>†</sup> | 20      |
| Euro OTC | Sodium edetate | 1609023-01 | 22950              | 40      |
| Euro OTC | Sodium edetate | 1704011    | 23390              | 40      |
| Caelo    | Sodium edetate | 172618     | 23663              | 40      |
| Caelo    | Sodium edetate | 15427714   | not required       | 13      |

- 146 536 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 259 spectra from 150 *Apo-Ident* customers from 89 batches from the substance/substance group *Sodium edetate*.

| Supplier             | Substance      | Batch                | Spectra |
|----------------------|----------------|----------------------|---------|
| Euro OTC             | Sodium edetate | 13142018             | 1       |
| Fagron               | Sodium edetate | 13K19-B02-290051     | 5       |
| Caelo                | Sodium edetate | 15116603             | 10      |
| Caelo                | Sodium edetate | 15427717             | 4       |
| Caelo                | Sodium edetate | 15427703             | 4       |
| Fagron               | Sodium edetate | 16F21-B02-323069     | 1       |
| Fagron               | Sodium edetate | 601EB174             | 1       |
| GEHE                 | Sodium edetate | 11074702             | 1       |
| Caelo                | Sodium edetate | 12181714             | 2       |
| Caelo                | Sodium edetate | 12E16-N04            | 1       |
| Fagron               | Sodium edetate | 914E-01925           | 1       |
| Fagron               | Sodium edetate | 13K19-B02            | 2       |
| Fagron               | Sodium edetate | 13I23-N03            | 8       |
| Fagron               | Sodium edetate | 13k19-b02-290051     | 2       |
| Fagron               | Sodium edetate | 601HA062             | 4       |
| Caelo                | Sodium edetate | 12181711             | 12      |
| Caelo                | Sodium edetate | 13142004             | 4       |
| Caelo                | Sodium edetate | 13142008             | 8       |
| Fagro/Gehe           | Sodium edetate | 601H1300             | 1       |
| Caelo                | Sodium edetate | 13/23-N03-3472312131 | 1       |
| Caelo                | Sodium edetate | 13142002             | 4       |
| Caelo                | Sodium edetate | 11074608             | 2       |
| Caelo                | Sodium edetate | 13142009             | 8       |
| Caelo                | Sodium edetate | 13142014             | 1       |
| Caelo                | Sodium edetate | 13142010             | 3       |
| Caelo                | Sodium edetate | 13142015             | 6       |
| Caelo                | Sodium edetate | 13395002             | 3       |
| phönix               | Sodium edetate | 13142018             | 1       |
| Caelo                | Sodium edetate | 13142018             | 1       |
| Caelo                | Sodium edetate | 13395007             | 5       |
| Caelo                | Sodium edetate | 14270505             | 3       |
| Caelo                | Sodium edetate | 13K19-B02-290051     | 1       |
| Fagron               | Sodium edetate | 13K19-B02-290052     | 3       |
| Caelo                | Sodium edetate | 14270506             | 3       |
| phönix               | Sodium edetate | 13K19-B02-290051     | 1       |
| Caelo                | Sodium edetate | 15427714             | 5       |
| Nachprüfung          | Sodium edetate | 601HA062             | 2       |
| Caelo                | Sodium edetate | 12181702             | 1       |
| Fagron               | Sodium edetate | 16F21-B02-324370     | 3       |
| Fagron               | Sodium edetate | 215I-01925           | 1       |
| Caelo                | Sodium edetate | 12G25-N12            | 1       |
| Fagron               | Sodium edetate | 13/23-N03            | 5       |
| Caelo                | Sodium edetate | 2101414              | 1       |
| Phönix               | Sodium edetate | 13E15-B10            | 1       |
| Fagron               | Sodium edetate | 13E15-N05            | 10      |
| Phönix               | Sodium edetate | 13G15-N03            | 1       |
| Caelo                | Sodium edetate | 13E15-N05            | 5       |
| Fagron               | Sodium edetate | 13E15-B10-289034     | 1       |
| Phoenix Goettin      | Sodium edetate | 13G15-N03            | 1       |
| Phoenix Goettin      | Sodium edetate | 13G15-N03            | 1       |
| Fagron               | Sodium edetate | 13I23-N03            | 1       |
| Fagron               | Sodium edetate | 13K19B02             | 1       |
| Fagron               | Sodium edetate | 13K19-B02-289035     | 1       |
| Fagron               | Sodium edetate | 13K19B02290051       | 1       |
| Fagron               | Sodium edetate | 13K-19-B02-290051    | 1       |
| Caesar & Loretz GmbH | Sodium edetate | 14270505             | 1       |

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| <b>Supplier</b>              | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|------------------------------|------------------|------------------|----------------|
| Caelo                        | Sodium edetate   | 1427006          | 1              |
| Caelo                        | Sodium edetate   |                  | 1              |
| Fagron                       | Sodium edetate   | 14G03-B05        | 5              |
| Fagron                       | Sodium edetate   | 14G03-B05307737  | 1              |
| Fagron                       | Sodium edetate   | 14G03-B05-307737 | 4              |
| Caelo                        | Sodium edetate   | 14G03-B05-307737 | 1              |
| Fagron                       | Sodium edetate   | 14G03B05309971   | 1              |
| Fagron                       | Sodium edetate   | 14G03-B05-309971 | 1              |
| Caelo                        | Sodium edetate   | 15035604         | 4              |
| Caelo                        | Sodium edetate   | 15035603         | 1              |
| Caelo                        | Sodium edetate   | 15116602         | 3              |
| Sanacorp                     | Sodium edetate   | 1505603          | 1              |
| Caelo                        | Sodium edetate   | 1517E-01925      | 1              |
| Phoenix                      | Sodium edetate   | 15427704         | 1              |
| Caelo                        | Sodium edetate   | 15427704         | 2              |
| Caelo                        | Sodium edetate   | 15427705         | 2              |
| Caesar & Loretz GmbH         | Sodium edetate   | 15427705         | 1              |
| Fagron                       | Sodium edetate   | 15D01-B05-315877 | 2              |
| Fagron                       | Sodium edetate   | 16F21-B02-325085 | 1              |
| Fagron                       | Sodium edetate   | 16F21-B02-327696 | 1              |
| Fagron                       | Sodium edetate   | 16F21-B02-329900 | 1              |
| Fagron                       | Sodium edetate   | 4114Q-01925      | 1              |
| Fagron                       | Sodium edetate   | 5315A-01925      | 1              |
| Caelo                        | Sodium edetate   | 11074611         | 1              |
| Fagron                       | Sodium edetate   | 813Q-01925       | 1              |
| Phönix                       | Sodium edetate   | 11074702         | 1              |
| Caelo                        | Sodium edetate   | 11074703         | 1              |
| Cranach-Apotheke             | Sodium edetate   | 11a31-no6        | 1              |
| phönix, 19.12.2012           | Sodium edetate   | 11L13-N02        | 1              |
| Caelo                        | Sodium edetate   | 12181704         | 1              |
| Caelo                        | Sodium edetate   | 12181703         | 3              |
| Fagron                       | Sodium edetate   | 11L13-N02        | 1              |
| Caelo                        | Sodium edetate   | 12181706         | 3              |
| Heidelberger/Noweda          | Sodium edetate   | 12181711         | 1              |
| Caelo                        | Sodium edetate   | 12254507         | 3              |
| Alliance Healthcare          | Sodium edetate   | 12181714         | 1              |
| Fagron                       | Sodium edetate   | 12E16-N04        | 2              |
| Sanacorp                     | Sodium edetate   | 12G25-N12        | 2              |
| Fagron                       | Sodium edetate   | 12G25-N12        | 5              |
| Fagron                       | Sodium edetate   | 12g25-n12        | 1              |
| Anzag, 24.10.2012            | Sodium edetate   | 12G25-W12        | 1              |
|                              | Sodium edetate   | 13142009         | 1              |
| sanacorp                     | Sodium edetate   | 13E15-N05        | 1              |
| Phönix                       | Sodium edetate   | 13E15-N05        | 3              |
| Gehe                         | Sodium edetate   | 13E15-N05        | 1              |
| Fagron                       | Sodium edetate   | 13E15-N05        | 2              |
| Sanacorp                     | Sodium edetate   | 13E15-N05        | 1              |
| Caelo                        | Sodium edetate   | 13E15-N05        | 1              |
| Fagron                       | Sodium edetate   | 13G15-N03        | 3              |
| Fagron                       | Sodium edetate   | 14G03-B05-30773  | 1              |
| Caelo                        | Sodium edetate   | 2913M1925        | 1              |
| Fagron                       | Sodium edetate   | 601H1300         | 2              |
| Gehe                         | Sodium edetate   | 601H1300         | 1              |
| Caelo                        | Sodium edetate   | 3211I-01925      | 1              |
| Sanacorp                     | Sodium edetate   | 6/AKD14          | 1              |
| Noweda                       | Sodium edetate   | 601H1300         | 1              |
| Caesar & Loretz GmbH, 4. . . | Sodium edetate   | 12181711         | 1              |
| Fagron                       | Sodium edetate   | 12E12-N04        | 1              |
| Phönix                       | Sodium edetate   | 13142004         | 1              |
| Caesar & Loretz GmbH         | Sodium edetate   | 13142008         | 1              |

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| Supplier | Substance      | Batch       | Spectra |
|----------|----------------|-------------|---------|
| Caelo    | Sodium edetate | 92159379    | 1       |
| Fagron   | Sodium edetate | 13E15-No5   | 1       |
| Fagron   | Sodium edetate | 5012Q-01925 | 1       |

- 69 374 spectra from 414 *Apo-Ident* customers from a total of 23 713 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sodium edetate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sodium edetate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 193           | 0              | 146 536       |
| <b>Type C</b> | 0              | 259           | 0              | 69 374        |

The substance/substance group *Sodium edetate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.8912 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 100.0000 % (> 97.6834 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20937     | 20937               | 0.00                         | 66.05                           |

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| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21362            | 22915                      | 4.37                                | 67.80                                  |
| 22465            | 22465                      | 0.00                                | 75.71                                  |
| 22915            | 22915                      | 0.00                                | 72.87                                  |
| 22926            | 22915                      | 4.54                                | 66.69                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Sodium methyl-4-hydroxybenzoate</b>                          |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 22602-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Sodium methyl-4-hydroxybenzoate; Methylis parahydroxybenzoas natricus; Natrium methylparahydroxybenzoicum

### Special notes

When selecting the *Sodium methyl-4-hydroxybenzoate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sodium methyl-4-hydroxybenzoate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate        |
|----------|---------------------|----------|-----------|---------|--------------------|
| Caelo    | Sodium methyl-4-... | 15358708 | 22602     | 40      | AR-16-FG-015095-01 |
| Caelo    | Sodium methyl-4-... | 15358709 | 22776     | 40      | 20151127           |
| Caelo    | Sodium methyl-4-... | 15358713 | 23093     | 40      | 20151127           |
| Caelo    | Sodium methyl-4-... | 170519   | 23289     | 40      | 20170308*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Sodium methyl-4-hydroxybenzoate*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 40 spectra of 1 reference samples from the substance/substance group *Sodium methyl-4-hydroxybenzoate*.

| Supplier | Substance                         | Batch    | Sample ID | Spectra |
|----------|-----------------------------------|----------|-----------|---------|
| Caelo    | Sodium methyl-4-hydroxybenzo. . . | 15358708 | 22603     | 40      |

- 146 689 spectra from a total of 3193 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Sodium methyl-4-hydroxybenzoate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sodium methyl-4-hydroxybenzoate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sodium methyl-4-hydroxybenzoate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 40            | 0              | 146 689       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Sodium methyl-4-hydroxybenzoate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 85.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22602     | 22602               | 0.00                         | 45.52                           |
| 22776     | 22602               | 10.10                        | 45.85                           |
| 23093     | 23289               | 7.85                         | 45.21                           |
| 23289     | 23289               | 0.00                         | 46.94                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe

von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sodium salicylate, powdered**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21037-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sodium salicylate, powdered; Natrii salicylas plv.; Natrii salicylicum plv.

### Special notes

When selecting the *Sodium salicylate, powdered* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sodium salicylate, powdered*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Sodium salicylat... | 12158307 | 21037     | 40      | 1403225     |
| Caelo    | Sodium salicylat... | 13140513 | 21689     | 40      | 20130531    |
| Caelo    | Sodium salicylat... | 163053   | 23052     | 40      | 20161118*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Sodium salicylate, powdered*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *Sodium salicylate, powdered*.

| Supplier | Substance                   | Batch    | Sample ID          | Spectra |
|----------|-----------------------------|----------|--------------------|---------|
| Caelo    | Sodium salicylate, powdered | 10176004 | 20284              | 40      |
| Caelo    | Sodium salicylate, powdered | 13140513 | 21689 <sup>†</sup> | 20      |
| Caelo    | Sodium salicylate, powdered | 16305301 | 22879              | 40      |

- 146 629 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 5 spectra from 5 *Apo-Ident* customers from 5 batches from the substance/substance group *Sodium salicylate, powdered*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier            | Substance                   | Batch         | Spectra |
|---------------------|-----------------------------|---------------|---------|
| Phoenix             | Sodium salicylate, powdered | 12158309      | 1       |
| Fagron              | Sodium salicylate, powdered | 102091210     | 1       |
| GATT-KOLLER/PHOENIX | Sodium salicylate, powdered | 4853/11124512 | 1       |
| Caelo               | Sodium salicylate, powdered | 18061305      | 1       |
| Fagron              | Sodium salicylate, powdered | 13G08-N07     | 1       |

- 69 628 spectra from 414 *Apo-Ident* customers from a total of 23 796 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sodium salicylate, powdered* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sodium salicylate, powdered* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 100           | 0              | 146 629       |
| <b>Type C</b> | 0              | 5             | 0              | 69 628        |

The substance/substance group *Sodium salicylate, powdered* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8815 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21037     | 21037               | 0.00                         | 89.12                           |
| 21689     | 21037               | 7.83                         | 90.16                           |
| 23052     | 23052               | 0.00                         | 87.00                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sodium tetraborate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20179-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sodium tetraborate; Borax; Natrii tetraboricum

### Special notes

When selecting the *Sodium tetraborate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sodium tetraborate*:

| Supplier | Substance          | Batch      | Sample ID | Spectra | Certificate |
|----------|--------------------|------------|-----------|---------|-------------|
| Caelo    | Sodium tetraborate | 13290118   | 21438     | 40      | 1412042     |
| Euro OTC | Sodium tetraborate | 1404025-01 | 21656     | 40      | 20140514    |
| Euro OTC | Sodium tetraborate | 1507024    | 21854     | 40      | 20150730*   |
| Euro OTC | Sodium tetraborate | 1510032    | 22235     | 40      | 20151118*   |
| Caelo    | Sodium tetraborate | 161372     | 22475     | 40      | 20160624*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Sodium tetraborate*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 310 spectra of 10 reference samples from the substance/substance group *Sodium tetraborate*.

| Supplier | Substance          | Batch      | Sample ID          | Spectra |
|----------|--------------------|------------|--------------------|---------|
| Euro OTC | Sodium tetraborate | 2905009-02 | 20179              | 50      |
| Caelo    | Sodium tetraborate | 13290118   | 21438 <sup>†</sup> | 20      |
| Euro OTC | Sodium tetraborate | 1404025-01 | 21656 <sup>†</sup> | 20      |
| Euro OTC | Sodium tetraborate | 1507024    | 21854 <sup>†</sup> | 20      |
| Euro OTC | Sodium tetraborate | 1510032    | 22235 <sup>†</sup> | 20      |
| Caelo    | Sodium tetraborate | 161372     | 22475 <sup>†</sup> | 20      |
| Euro OTC | Sodium tetraborate | 1603043    | 22508              | 40      |
| Caelo    | Sodium tetraborate | 161372     | 22621              | 40      |
| Euro OTC | Sodium tetraborate | 1607036    | 22713              | 40      |
| Euro OTC | Sodium tetraborate | 1701046    | 22990              | 40      |

- 146 419 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 26 spectra from 16 *Apo-Ident* customers from 18 batches from the substance/substance group *Sodium tetraborate*.

| Supplier              | Substance          | Batch         | Spectra |
|-----------------------|--------------------|---------------|---------|
| Caelo                 | Sodium tetraborate | 11369431      | 1       |
| Caelo                 | Sodium tetraborate | 1309032-01    | 1       |
| Caelo                 | Sodium tetraborate | 13290118      | 1       |
| Euro OTC              | Sodium tetraborate | 1404025-01    | 4       |
| Caelo                 | Sodium tetraborate | 14310905      | 2       |
| Productos Quimicos    | Sodium tetraborate | 16000597      | 1       |
| Caelo                 | Sodium tetraborate | 21051402      | 1       |
| Euro OTC              | Sodium tetraborate | 1402002-01    | 2       |
| Euro OTC              | Sodium tetraborate | 1408006-01    | 2       |
| Euro OTC              | Sodium tetraborate | 1503043-01    | 1       |
| Euro OTC              | Sodium tetraborate | 1507024-01    | 2       |
| Phoenix               | Sodium tetraborate | 1603043-01    | 1       |
| Fagron                | Sodium tetraborate | 12H09-N03     | 1       |
| Euro OTC              | Sodium tetraborate | 1607036-01    | 1       |
| Euro OTC              | Sodium tetraborate | 1302034-01    | 1       |
| Euro OTC              | Sodium tetraborate | 13111207      | 1       |
| Euro OTC              | Sodium tetraborate | 130203401     | 1       |
| Euro OTC              | Sodium tetraborate | 1309032-01    | 1       |
| Gatt-Koller / Phoenix | Sodium tetraborate | 6187/01142114 | 1       |

- 69 607 spectra from 414 *Apo-Ident* customers from a total of 23 785 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sodium tetraborate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sodium tetraborate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 196           | 4              | 71 186        |
| <b>Type B</b> | 0              | 301           | 9              | 146 419       |
| <b>Type C</b> | 0              | 26            | 0              | 69 607        |

The substance/substance group *Sodium tetraborate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 98.0000 % (> 96.5000 %)  |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 97.0968 % (> 96.1290 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 76.9231 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21438     | 21438               | 0.00                         | 44.89                           |
| 21656     | 21438               | 6.77                         | 45.97                           |
| 21854     | 21854               | 0.00                         | 45.97                           |
| 22235     | 22235               | 0.00                         | 45.10                           |
| 22475     | 22475               | 0.00                         | 46.92                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sorbic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20881-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sorbic acid; Acidum sorbicum; Acidum sorbinicum

### Special notes

When selecting the *Sorbic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sorbic acid*:

| Supplier | Substance   | Batch    | Sample ID | Spectra | Certificate        |
|----------|-------------|----------|-----------|---------|--------------------|
| Caelo    | Sorbic acid | 12038025 | 20881     | 40      | 20120315           |
| Caelo    | Sorbic acid | 13334008 | 21460     | 40      | AR-15-FG-007849-01 |
| Caelo    | Sorbic acid | 14176214 | 22592     | 40      | 20140708           |
| Caelo    | Sorbic acid | 15382002 | 22826     | 40      | 20151112           |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Sorbic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 100 spectra of 3 reference samples from the substance/substance group *Sorbic acid*.

| Supplier | Substance   | Batch    | Sample ID          | Spectra |
|----------|-------------|----------|--------------------|---------|
| Caelo    | Sorbic acid | 13334008 | 21460 <sup>†</sup> | 20      |
| Caelo    | Sorbic acid | 14380714 | 22593              | 40      |
| Caelo    | Sorbic acid | 162080   | 22616              | 40      |

- 146 629 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 161 spectra from 103 *Apo-Ident* customers from 49 batches from the substance/substance group *Sorbic acid*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                  | Substance   | Batch         | Spectra |
|---------------------------|-------------|---------------|---------|
| vdl 28.04.2014 preis:5,79 | Sorbic acid |               | 1       |
| Caelo                     | Sorbic acid | 13334008      | 5       |
| VDL;5,78EUR;18.12         | Sorbic acid | 14176206      | 1       |
| Caelo                     | Sorbic acid | 14176206      | 9       |
| Caelo                     | Sorbic acid | 14176209      | 4       |
| Caelo                     | Sorbic acid | 14176214      | 6       |
| Caelo                     | Sorbic acid | 12038016      | 6       |
| Caelo                     | Sorbic acid | 12038025      | 1       |
| Caelo                     | Sorbic acid | 12330608      | 8       |
| Caelo                     | Sorbic acid | 12330618      | 13      |
| Caelo                     | Sorbic acid | 4811Q-01048   | 1       |
| Caelo                     | Sorbic acid | 12038003      | 3       |
| Fagron                    | Sorbic acid | 12330618      | 1       |
| Caelo                     | Sorbic acid | 13334003      | 4       |
| Caelo                     | Sorbic acid | 13334010      | 5       |
| PHOENIX 12.05.2014        | Sorbic acid | 13334008      | 1       |
| Caelo                     | Sorbic acid | 13334015      | 1       |
| Fagron                    | Sorbic acid | 14176206      | 1       |
| Caelo                     | Sorbic acid | 14176207      | 1       |
| Caelo                     | Sorbic acid | 14176212      | 4       |
| Caelo                     | Sorbic acid | 14176213      | 1       |
| Caelo                     | Sorbic acid | 14380702      | 3       |
| Caelo                     | Sorbic acid | 14380706      | 4       |
| Caelo                     | Sorbic acid | 14380704      | 1       |
| Caelo                     | Sorbic acid | 14380713      | 2       |
| Caelo                     | Sorbic acid | 14380714      | 6       |
| Gatt-Koller / Phoenix     | Sorbic acid | 2575/07142914 | 1       |
| Caesar & Loretz/Noweda    | Sorbic acid | 14380706      | 1       |
| Caelo                     | Sorbic acid | 15382002      | 4       |
| Caelo                     | Sorbic acid | 15382007      | 3       |
| Caelo                     | Sorbic acid | 15382010      | 3       |
| Caelo                     | Sorbic acid | 16208005      | 4       |
| Caelo                     | Sorbic acid | 16208009      | 3       |
| Caelo                     | Sorbic acid | 16208015      | 1       |
| Euro OTC                  | Sorbic acid | o216E-01048   | 1       |
| Caelo                     | Sorbic acid | 10120303      | 1       |
| Caelo                     | Sorbic acid | 213E-01048    | 1       |
| Caelo                     | Sorbic acid | 10305208      | 1       |
| Caelo                     | Sorbic acid | 9280207       | 1       |
| Finze                     | Sorbic acid | 9280207       | 1       |
| Caelo                     | Sorbic acid | 10305209      | 1       |
| Caelo                     | Sorbic acid | 10305213      | 2       |
| Caelo                     | Sorbic acid | 11203806      | 3       |
| Caelo                     | Sorbic acid | 11203807      | 11      |
| Caelo                     | Sorbic acid | 105505        | 1       |
| Caelo                     | Sorbic acid | 11203812      | 1       |
| Phoenix                   | Sorbic acid | 11203813      | 1       |
| Caelo                     | Sorbic acid | 12038002      | 2       |
| Caelo                     | Sorbic acid | 12038009      | 1       |
| Caelo                     | Sorbic acid | 12038012      | 1       |
| Phönix                    | Sorbic acid | 1171          | 1       |
| Sanacorp                  | Sorbic acid | 12038016      | 1       |
| Anzag                     | Sorbic acid | 12038016      | 1       |
| Noweda                    | Sorbic acid | 12038016      | 1       |
| Noweda                    | Sorbic acid | 12038020      | 1       |
| Caelo                     | Sorbic acid | 12038020      | 6       |
| Euro OTC                  | Sorbic acid | 12038020      | 1       |
| Fagron                    | Sorbic acid | 121394        | 1       |
| Noweda                    | Sorbic acid | 12330608      | 1       |
| Phönix                    | Sorbic acid | 12330618      | 1       |

*continued on the next page*



continued from previous page

| Supplier | Substance   | Batch       | Spectra |
|----------|-------------|-------------|---------|
| Sanacorp | Sorbic acid | 13334008    | 1       |
| Caelo    | Sorbic acid | 29071201    | 1       |
| Caelo    | Sorbic acid | 5012E-01048 | 1       |

- 69 472 spectra from 414 *Apo-Ident* customers from a total of 23 752 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sorbic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sorbic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 100           | 0              | 146 629       |
| <b>Type C</b> | 0              | 118           | 43             | 69 472        |

The substance/substance group *Sorbic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 73.2919 % (> 71.4286 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20881     | 21460               | 5.06                         | 48.70                           |
| 21460     | 21460               | 0.00                         | 48.58                           |
| 22592     | 21460               | 7.68                         | 49.76                           |
| 22826     | 21460               | 7.27                         | 47.23                           |



Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sorbitol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20075-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sorbitol; Sorbitolum

### Special notes

When selecting the *Sorbitol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sorbitol*:

| Supplier | Substance | Batch    | Sample ID | Spectra | Certificate |
|----------|-----------|----------|-----------|---------|-------------|
| Caelo    | Sorbitol  | 13278217 | 21485     | 40      | 20130920    |
| Euro OTC | Sorbitol  | 1506052  | 21834     | 40      | 20150713*   |
| Euro OTC | Sorbitol  | 1512016  | 22293     | 40      | 20160113*   |
| Euro OTC | Sorbitol  | 1604007  | 22539     | 40      | 20160428*   |
| Caelo    | Sorbitol  | 16038501 | 22847     | 40      | 20160315    |
| Euro OTC | Sorbitol  | 1610018  | 22849     | 40      | 20161121*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 240 spectra of 6 reference samples from the substance/substance group *Sorbitol*. These samples are listed above in the [calibration samples](#) section.
- 71 146 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 205 spectra of 6 reference samples from the substance/substance group *Sorbitol*.

| Supplier | Substance | Batch    | Sample ID          | Spectra |
|----------|-----------|----------|--------------------|---------|
| Caelo    | Sorbitol  | 91992409 | 20075              | 45      |
| Caelo    | Sorbitol  | 11379309 | 20499              | 40      |
| Euro OTC | Sorbitol  | 1506052  | 21834 <sup>†</sup> | 20      |
| Euro OTC | Sorbitol  | 1512016  | 22293 <sup>†</sup> | 20      |
| Caelo    | Sorbitol  | 163531   | 23028              | 40      |
| Caelo    | Sorbitol  | 16353107 | 23442              | 40      |

- 146 524 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 154 spectra from 54 *Apo-Ident* customers from 89 batches from the substance/substance group *Sorbitol*.

| Supplier           | Substance | Batch             | Spectra |
|--------------------|-----------|-------------------|---------|
| Caelo              | Sorbitol  | 5021307           | 1       |
| Caelo              | Sorbitol  | 11379336          | 2       |
| Fagron             | Sorbitol  |                   | 1       |
| Fagron             | Sorbitol  | 12J15-N01         | 1       |
| Caelo              | Sorbitol  | 13278216          | 3       |
| Fagron             | Sorbitol  | 12L17-N12         | 3       |
| Caelo              | Sorbitol  | 13278241          | 1       |
| Gehe 01.09.2014    | Sorbitol  | 13278217          | 1       |
| Caelo              | Sorbitol  | 13278249          | 1       |
| Caelo              | Sorbitol  | 13278250          | 1       |
| Fagron             | Sorbitol  | 13D08-N27         | 1       |
| Caelo              | Sorbitol  | 13335307          | 3       |
| Caelo              | Sorbitol  | 15118901          | 6       |
| Caelo              | Sorbitol  | 14250807          | 1       |
| Caelo              | Sorbitol  | 15208310          | 4       |
| Caelo              | Sorbitol  | 16038515          | 3       |
| Caelo              | Sorbitol  | 16101303          | 1       |
| Euro OTC           | Sorbitol  | 1604007-01        | 2       |
| Caelo              | Sorbitol  | 22011305          | 1       |
| Fagron             | Sorbitol  | M721140/12L17-N12 | 1       |
| Caelo              | Sorbitol  | 4091401           | 1       |
| Caelo              | Sorbitol  | 8081402           | 1       |
| Phönix Gotha       | Sorbitol  | 10383330          | 1       |
| Caelo              | Sorbitol  | 1083330           | 2       |
| Phönix 05.11.2012  | Sorbitol  | 1112010-01        | 1       |
| Caelo              | Sorbitol  | 11379320          | 1       |
| Caelo              | Sorbitol  | 11379321          | 1       |
| Caelo              | Sorbitol  | 11379322          | 1       |
| Phönix Gotha       | Sorbitol  | 11379332          | 1       |
| Caelo              | Sorbitol  | 11379332          | 3       |
| Caelo              | Sorbitol  | 11379337          | 2       |
| Caelo              | Sorbitol  | 12249108          | 2       |
| Fagron             | Sorbitol  | 11I09-N11         | 1       |
| Phoenix 12.08.2013 | Sorbitol  | 12249108          | 1       |
| Caelo              | Sorbitol  | 12249109          | 2       |
| Caelo              | Sorbitol  | 12249110          | 4       |
| Caelo              | Sorbitol  | 12249124          | 2       |
| Caelo              | Sorbitol  | 12249126          | 2       |
| Caelo              | Sorbitol  | 12249139          | 1       |
| Caelo              | Sorbitol  | 12249140          | 1       |
| Caelo              | Sorbitol  |                   | 1       |
| Caelo              | Sorbitol  | 12345             | 1       |
| Fagron             | Sorbitol  | 12E30-N24         | 5       |
| Euro OTC           | Sorbitol  | 1301019-01        | 2       |
| Caelo              | Sorbitol  | 12L07-N12         | 1       |
| Caelo              | Sorbitol  | 13278204          | 1       |
| Euro OTC           | Sorbitol  | 1311034-01        | 1       |
| eurho              | Sorbitol  | 1301019-01        | 1       |
| Bombastus          | Sorbitol  | 13278206          | 2       |
| Caelo              | Sorbitol  | 13278206          | 1       |
| Caelo              | Sorbitol  | 13278218          | 1       |
| Caelo              | Sorbitol  | 13278239          | 1       |
| GEHE 28.11.2014    | Sorbitol  | 13278245          | 1       |
| Caelo              | Sorbitol  | 13278247          | 1       |
| Caelo              | Sorbitol  | 13278246          | 3       |
| Fagron             | Sorbitol  | 13278249          | 1       |

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| Supplier              | Substance | Batch         | Spectra |
|-----------------------|-----------|---------------|---------|
| Caelo                 | Sorbitol  | 13335304      | 2       |
| Caelo                 | Sorbitol  | 13335307      | 1       |
| Merck                 | Sorbitol  | 13D08-N27     | 1       |
| Fagron                | Sorbitol  | 13E07-B40     | 2       |
| Gehe                  | Sorbitol  | 1404007-01    | 1       |
| Fagron                | Sorbitol  | 13G04-N04     | 1       |
| Euro OTC              | Sorbitol  | 1404007-01    | 4       |
| Caelo                 | Sorbitol  | 14250806      | 1       |
| Caelo                 | Sorbitol  | 14250808      | 1       |
| Fagron                | Sorbitol  | 14E21-B02     | 1       |
| Euro OTC              | Sorbitol  | 1501048-01    | 3       |
| Caelo                 | Sorbitol  | 15012708      | 1       |
| Euro OTC              | Sorbitol  | 1506052-01    | 4       |
| Caelo                 | Sorbitol  | 15118902      | 2       |
| Caelo                 | Sorbitol  | 15118912      | 1       |
| Euro OTC              | Sorbitol  | 1512016-01    | 1       |
| Caelo                 | Sorbitol  | 15208302      | 2       |
| Caelo                 | Sorbitol  | 15208303      | 1       |
| Caelo                 | Sorbitol  | 15208305      | 3       |
| Caelo                 | Sorbitol  | 15208306      | 1       |
| Caelo                 | Sorbitol  | 15208309      | 2       |
| Caelo                 | Sorbitol  | 15208311      | 3       |
| Caelo                 | Sorbitol  | 16038501      | 3       |
| Caelo                 | Sorbitol  | 16038503      | 1       |
| Caelo                 | Sorbitol  | 16038514      | 2       |
| Euro OTC              | Sorbitol  | 1610018-01    | 1       |
| Caelo                 | Sorbitol  | 16353102      | 1       |
| Caelo                 | Sorbitol  | 17011305      | 1       |
| Gatt-Koller / Phoenix | Sorbitol  | 1718/0513     | 1       |
| Gatt-Koller / Phoenix | Sorbitol  | 1718/05134013 | 1       |
| Caelo                 | Sorbitol  | 20021501      | 1       |
| Caelo                 | Sorbitol  | 23071201      | 1       |
| Caelo                 | Sorbitol  | 23081401      | 1       |
| Caelo                 | Sorbitol  | 26071402      | 1       |
| EuRho/Anzag           | Sorbitol  | 4712I-02298   | 1       |
| Euro OTC              | Sorbitol  | 700476        | 1       |
| Fagron                | Sorbitol  | M721140       | 1       |
| Caelo                 | Sorbitol  | 10383323      | 1       |
| Caelo                 | Sorbitol  | 13335302      | 1       |
| Euro OTC              | Sorbitol  | 150652-01     | 1       |
| Euro OTC              | Sorbitol  | 1406014-01    | 1       |

- 69 479 spectra from 414 *Apo-Ident* customers from a total of 23 715 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sorbitol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sorbitol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 240           | 0              | 71 146        |
| Type B | 0              | 205           | 0              | 146 524       |
| Type C | 0              | 149           | 5              | 69 479        |

The substance/substance group *Sorbitol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.0732 %) |
| Type C | 100.0000 % (> 99.8813 %) | 96.7532 % (> 94.8052 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21485     | 21834               | 4.67                         | 40.60                           |
| 21834     | 21834               | 0.00                         | 38.56                           |
| 22293     | 22293               | 0.00                         | 38.75                           |
| 22539     | 22539               | 0.00                         | 40.06                           |
| 22847     | 21834               | 2.86                         | 40.33                           |
| 22849     | 22849               | 0.00                         | 37.41                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Soy lecithin (instant form)</b>                              |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20539-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Soy lecithin (instant form); Lecithinum e sojæ plv.

### Special notes

When selecting the *Soy lecithin (instant form)* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Soy lecithin (instant form)*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Soy lecithin (in... | 13030504 | 20985     | 40      | 1404399     |
| Caelo    | Soy lecithin (in... | 13279813 | 21523     | 40      | 20130903    |
| Caelo    | Soy lecithin (in... | 17118101 | 23370     | 40      | 20170620    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Soy lecithin (instant form)*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 3 reference samples from the substance/substance group *Soy lecithin (instant form)*.

| Supplier | Substance                   | Batch    | Sample ID | Spectra |
|----------|-----------------------------|----------|-----------|---------|
| Caelo    | Soy lecithin (instant form) | 11145311 | 20448     | 40      |
| Caelo    | Soy lecithin (instant form) | 11371501 | 20539     | 40      |
| Caelo    | Soy lecithin (instant form) | 17118101 | 23445     | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 36 spectra from 18 *Apo-Ident* customers from 24 batches from the substance/substance group *Soy lecithin (instant form)*.

| Supplier | Substance                   | Batch    | Spectra |
|----------|-----------------------------|----------|---------|
| Caelo    | Soy lecithin (instant form) | 13279806 | 1       |
| Caelo    | Soy lecithin (instant form) | 14281605 | 1       |
| Caelo    | Soy lecithin (instant form) | 14281620 | 1       |
| Caelo    | Soy lecithin (instant form) | 11145311 | 1       |

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| Supplier                   | Substance                   | Batch    | Spectra |
|----------------------------|-----------------------------|----------|---------|
| Caelo                      | Soy lecithin (instant form) | 13030506 | 1       |
| Caelo                      | Soy lecithin (instant form) | 11371502 | 1       |
| Caelo                      | Soy lecithin (instant form) | 12139012 | 1       |
| Caesar & Loretz GmbH       | Soy lecithin (instant form) | 13279813 | 1       |
| Caelo                      | Soy lecithin (instant form) | 14196305 | 1       |
| Sanacorp                   | Soy lecithin (instant form) | 14196305 | 1       |
| Caesar & Loretz GmbH       | Soy lecithin (instant form) | 14281603 | 1       |
| Caelo                      | Soy lecithin (instant form) | 14281618 | 4       |
| Caelo                      | Soy lecithin (instant form) | 15262701 | 2       |
| Caelo                      | Soy lecithin (instant form) | 11371504 | 1       |
| Caelo                      | Soy lecithin (instant form) | 12139001 | 4       |
| Caelo                      | Soy lecithin (instant form) | 1526704  | 1       |
| siehe WE-Prüfprotokoll     | Soy lecithin (instant form) | 31/14    | 1       |
| Caesar & Loretz GmbH, 4... | Soy lecithin (instant form) | 12139013 | 1       |
| Caelo                      | Soy lecithin (instant form) | 12139011 | 3       |
| Caelo                      | Soy lecithin (instant form) | 12139002 | 1       |
| Caelo                      | Soy lecithin (instant form) | 12139008 | 1       |
| Caelo                      | Soy lecithin (instant form) | 12139013 | 1       |
| Caelo                      | Soy lecithin (instant form) |          | 1       |
| Caelo                      | Soy lecithin (instant form) | 13030503 | 1       |
| Caesar & Loretz GmbH       | Soy lecithin (instant form) | 13030503 | 1       |
| Caelo                      | Soy lecithin (instant form) | 13279814 | 1       |
| Caelo                      | Soy lecithin (instant form) | 13279804 | 1       |

- 69 597 spectra from 414 *Apo-Ident* customers from a total of 23 778 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Soy lecithin (instant form)* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Soy lecithin (instant form)* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 85            | 35             | 146 609       |
| <b>Type C</b> | 0              | 33            | 3              | 69 597        |

The substance/substance group *Soy lecithin (instant form)* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 70.8333 % (> 68.3333 %)  |
| <b>Type C</b> | 100.0000 % (> 99.9813 %) | 91.6667 % (> 83.3333 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several

new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20985     | 20985               | 0.00                         | 48.13                           |
| 21523     | 20985               | 11.34                        | 53.00                           |
| 23370     | 20985               | 7.47                         | 51.97                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Spironolactone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21032-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Spironolactone; Spironolactonum

### Special notes

When selecting the *Spironolactone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Spironolactone*:

| Supplier | Substance      | Batch                 | Sample ID | Spectra | Certificate |
|----------|----------------|-----------------------|-----------|---------|-------------|
| Euro OTC | Spironolactone | 1212034-01            | 21032     | 42      | 1403151     |
| Euro OTC | Spironolactone | 1602006               | 22369     | 30      | 20160309*   |
| Caelo    | Spironolactone | 14378715              | 22385     | 40      | 20150211    |
| Fagron   | Spironolactone | 2294216E20-B06-322016 | 22942     | 40      | 20160531    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 152 spectra of 4 reference samples from the substance/substance group *Spironolactone*. These samples are listed above in the [calibration samples](#) section.
- 71 234 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 355 spectra of 9 reference samples from the substance/substance group *Spironolactone*.

| Supplier | Substance      | Batch            | Sample ID          | Spectra |
|----------|----------------|------------------|--------------------|---------|
| Euro OTC | Spironolactone | 1004035-01       | 20180              | 50      |
| Euro OTC | Spironolactone | 1212034-01       | 21076              | 40      |
| Euro OTC | Spironolactone | 1602006          | 22369 <sup>†</sup> | 15      |
| Fagron   | Spironolactone | 15G22-B10-311159 | 22386              | 40      |
| Caelo    | Spironolactone | 160773           | 22444              | 60      |
| Euro OTC | Spironolactone | 1612002          | 22909              | 40      |
| Caelo    | Spironolactone | 16077305         | 22954              | 40      |
| Caelo    | Spironolactone | 171165           | 23327              | 40      |
| Caelo    | Spironolactone | 172432           | 23660              | 30      |

- 146 374 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 173 spectra from 75 *Apo-Ident* customers from 80 batches from the substance/substance group *Spironolactone*.

| Supplier           | Substance      | Batch            | Spectra |
|--------------------|----------------|------------------|---------|
| Caelo              | Spironolactone | 12049130         | 2       |
| Caelo              | Spironolactone | 10H24-N10        | 2       |
| Gutenberg-Apotheke | Spironolactone | 12049130         | 2       |
| Sanacorp           | Spironolactone | 1212034-01       | 1       |
| Caesar/Lorenz      | Spironolactone | 13124303         | 1       |
| Caelo              | Spironolactone | 13124304         | 6       |
| Caelo              | Spironolactone | 13124303         | 7       |
| Euro OTC           | Spironolactone | 1212034-01       | 4       |
| Caelo              | Spironolactone | 13124309         | 5       |
| Caelo              | Spironolactone | 13124315         | 6       |
| Caelo              | Spironolactone | 13124314         | 2       |
| Sanacorp/Phoenix   | Spironolactone | 13124315         | 3       |
| Caelo              | Spironolactone | 13124317         | 5       |
| Caelo              | Spironolactone | 13124321         | 2       |
| Caelo              | Spironolactone | 1314309          | 1       |
| Caelo              | Spironolactone | 13190309         | 1       |
| Fagron             | Spironolactone | 13G03-N09        | 1       |
| Caelo              | Spironolactone | 140202901        | 1       |
| Fagron             | Spironolactone | 13G16-B08        | 1       |
| Fagron             | Spironolactone |                  | 1       |
| Euro OTC           | Spironolactone | 1402029-01       | 1       |
| Fagron             | Spironolactone | 13G16-B08-288051 | 1       |
| Noweda             | Spironolactone | 14378702         | 1       |
| Caelo              | Spironolactone | 14378702         | 2       |
| Caelo              | Spironolactone | 1437807          | 1       |
| Caelo              | Spironolactone | 14378703         | 1       |
| Caelo              | Spironolactone | 14378707         | 2       |
| Caelo              | Spironolactone | 14378709         | 2       |
| Caelo              | Spironolactone | 14378710         | 2       |
| Jenne              | Spironolactone | 14378715         | 1       |
| Noweda             | Spironolactone | 14378710         | 1       |
| Caelo              | Spironolactone | 14378715         | 3       |
| Caelo              | Spironolactone | 14378717         | 3       |
| Stumpf             | Spironolactone | 14378718         | 1       |
| Caelo              | Spironolactone | 14378718         | 2       |
| Caelo              | Spironolactone | 14378719         | 1       |
| Caelo              | Spironolactone | 14378721         | 1       |
| Fagron             | Spironolactone | 14B20-B06-294618 | 5       |
| Fagron             | Spironolactone | 14B20B06294618   | 1       |
| Fagron             | Spironolactone | 14J02-B02-303621 | 5       |
| Euro OTC           | Spironolactone | 1504016-01       | 1       |
| Caelo              | Spironolactone | 150401601        | 1       |
| Fagron             | Spironolactone | 14J02-B303621    | 1       |
| Caelo              | Spironolactone | 16077302         | 5       |
| Caelo              | Spironolactone | 15G22-B10        | 1       |
| Caelo              | Spironolactone | 16077303         | 6       |
| Caelo              | Spironolactone | 16077305         | 2       |
| Caelo              | Spironolactone | 16077306         | 2       |
| Caelo              | Spironolactone | 16077309         | 2       |
| Caelo              | Spironolactone | 16077311         | 1       |
| Caelo              | Spironolactone | 16077312         | 2       |
| Fagron             | Spironolactone | 16E20-B06-322016 | 1       |

*continued on the next page*

continued from previous page

| Supplier              | Substance      | Batch            | Spectra |
|-----------------------|----------------|------------------|---------|
| Caelo                 | Spironolactone | 16077320         | 1       |
| Fagron                | Spironolactone | 16E20-B06-325478 | 1       |
| Fagron                | Spironolactone | 16I06-B04        | 1       |
| Caelo                 | Spironolactone | 5013Q-03249      | 1       |
| Fagron                | Spironolactone | 2415E-03249      | 1       |
| Fagron                | Spironolactone | ELN151105-2      | 1       |
| Euro OTC              | Spironolactone | 1004035          | 1       |
| Fagron                | Spironolactone | 80616-7          | 1       |
| Caelo                 | Spironolactone | 10159914         | 1       |
| Euro OTC              | Spironolactone | 1101013-01       | 1       |
| Euro OTC              | Spironolactone | 1004035-01       | 1       |
| Noweda                | Spironolactone | 1101013-0        | 1       |
| Caesar&loretz,Phoenix | Spironolactone | 11042603         | 1       |
| ANZAG am 10.05.2012   | Spironolactone | 11042607         | 1       |
| Phönix                | Spironolactone | 1101013-03       | 1       |
| Caelo                 | Spironolactone | 11042602         | 1       |
| Caelo                 | Spironolactone | 11042607         | 1       |
| Sanacorp              | Spironolactone | 11042612         | 1       |
| EuRho                 | Spironolactone | 1101013-01       | 1       |
| Caesar&loretz,Phoenix | Spironolactone | 11042613         | 1       |
| Fagron                | Spironolactone | 12/17-n01        | 1       |
| Sanacorp              | Spironolactone | 12049103         | 2       |
| Fagron                | Spironolactone | 12/17-N01        | 1       |
| Caelo                 | Spironolactone | 11G28-N03        | 1       |
| Gehe                  | Spironolactone | 12049105         | 1       |
| Caelo                 | Spironolactone | 12049103         | 1       |
| Caelo                 | Spironolactone | 12049109         | 1       |
| Caelo                 | Spironolactone | 12049105         | 2       |
| Phönix                | Spironolactone | 12049109         | 1       |
| Caelo                 | Spironolactone | 12049118         | 4       |
| Caelo                 | Spironolactone | 12049110         | 2       |
| Caesar u Loretz       | Spironolactone | 12049119         | 1       |
| Alliance Healthcare   | Spironolactone | 12049119         | 1       |
| Caelo                 | Spironolactone | 12049123         | 4       |
| Caesar & Loretz GmbH  | Spironolactone | 12049129         | 1       |
| Sanacorp              | Spironolactone | 12049130         | 1       |
| Caelo                 | Spironolactone | 12049129         | 1       |
| Alliance Healthcare   | Spironolactone | 12049129         | 1       |
| Fagron                | Spironolactone | 12I17-N01        | 1       |
| Caesar&loretz,Anzag   | Spironolactone | 13124309         | 1       |
| Gehe                  | Spironolactone | 13D12-N08        | 1       |
| Fagron                | Spironolactone | 13D12-N08        | 1       |
| Fagron                | Spironolactone | 16A14-B05-317123 | 1       |
| Caelo                 | Spironolactone | 2013U-03249      | 1       |
| Gehe                  | Spironolactone | 11B07-N06        | 2       |
| Euro OTC              | Spironolactone | 3513E-03249      | 1       |
| Fagron                | Spironolactone | 12J15-N04        | 1       |

- 69 460 spectra from 414 *Apo-Ident* customers from a total of 23 721 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).



## Validation results

The validation runs checked whether the substance/substance group *Spironolactone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Spironolactone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 152           | 0              | 71 234        |
| <b>Type B</b> | 0              | 335           | 20             | 146 374       |
| <b>Type C</b> | 0              | 166           | 7              | 69 460        |

The substance/substance group *Spironolactone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.0526 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 94.3662 % (> 93.5211 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 95.9538 % (> 94.2197 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21032     | 21032               | 0.00                         | 36.30                           |
| 22369     | 22369               | 0.00                         | 36.01                           |
| 22385     | 22369               | 21.18                        | 34.51                           |
| 22942     | 21032               | 4.02                         | 35.74                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Spray-dried arabic gum</b>                                   |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20457-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Spray-dried arabic gum; Acaciae gummi dispersione desiccatum; Gummi arabicum dispersione desiccatum

### Special notes

When selecting the *Spray-dried arabic gum* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Spray-dried arabic gum*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate        |
|----------|---------------------|----------|-----------|---------|--------------------|
| Caelo    | Spray-dried arab... | 14141901 | 21431     | 80      | AR-15-FG-006809-01 |
| Caelo    | Spray-dried arab... | 15413201 | 22653     | 40      | AR-17-FG-000844-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 2 reference samples from the substance/substance group *Spray-dried arabic gum*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 5 reference samples from the substance/substance group *Spray-dried arabic gum*.

| Supplier | Substance              | Batch    | Sample ID          | Spectra |
|----------|------------------------|----------|--------------------|---------|
| Caelo    | Spray-dried arabic gum | 11345708 | 20457              | 40      |
| Caelo    | Spray-dried arabic gum | 14141901 | 21431 <sup>†</sup> | 40      |
| Caelo    | Spray-dried arabic gum | 162331   | 22853              | 40      |
| Caelo    | Spray-dried arabic gum | 16233105 | 23443              | 40      |
| Caelo    | Spray-dried arabic gum | 16233105 | 23444              | 40      |

- 146 529 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 8 spectra from 8 *Apo-Ident* customers from 7 batches from the substance/substance group *Spray-dried arabic gum*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance              | Batch    | Spectra |
|----------|------------------------|----------|---------|
| Caelo    | Spray-dried arabic gum | 15086704 | 1       |
| Caelo    | Spray-dried arabic gum | 12111301 | 1       |
| Caelo    | Spray-dried arabic gum | 11345715 | 1       |
| Caelo    | Spray-dried arabic gum | 12138607 | 2       |
| Caelo    | Spray-dried arabic gum | 12372302 | 1       |
| Caelo    | Spray-dried arabic gum | 15413201 | 1       |
| Caelo    | Spray-dried arabic gum | 12138612 | 1       |

- 69 625 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Spray-dried arabic gum* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Spray-dried arabic gum* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 199           | 1              | 146 529       |
| <b>Type C</b> | 0              | 7             | 1              | 69 625        |

The substance/substance group *Spray-dried arabic gum* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.5000 % (> 98.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21431     | 21431               | 0.00                         | 15.49                           |
| 22653     | 22653               | 0.00                         | 15.05                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Starch**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20790-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Starch; Amylum Maydis; Amylum oryzae; Amylum Solani; Amylum tritici; Corn starch; Maydis amyllum; Oryzae amyllum; Potato starch; Rice starch; Solani amyllum; Tritici amyllum; Wheat starch

### Special notes

When selecting the *Starch* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Starch*:

| Supplier | Substance     | Batch    | Sample ID | Spectra | Certificate        |
|----------|---------------|----------|-----------|---------|--------------------|
| Caelo    | Rice starch   | 12068525 | 20790     | 40      | 20120327           |
| Caelo    | Potato starch | 12360213 | 20996     | 40      | 1403494            |
| Caelo    | Wheat starch  | 14023203 | 21447     | 40      | AR-16-FG-011433-01 |
| Caelo    | Corn starch   | 13154914 | 21827     | 40      | 20130529           |

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| Supplier | Substance     | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------|------------------|-----------|---------|--------------------|
| Caelo    | Potato starch | 14033815         | 21965     | 40      | 20140207           |
| Klenk    | Wheat starch  | 0104A141114      | 21973     | 40      | 20141210           |
| Caelo    | Wheat starch  | 15124707         | 22246     | 40      | 20150527           |
| Caelo    | Potato starch | 161237           | 22449     | 40      | 20160621*          |
| Caelo    | Corn starch   | 161385           | 22450     | 40      | 20160621*          |
| Caelo    | Rice starch   | 16144501         | 22585     | 40      | 20160504           |
| Caelo    | Rice starch   | 162180           | 22642     | 40      | 20160901*          |
| Fagron   | Rice starch   | 16B25-B01-327231 | 23220     | 40      | AR-17-FG-015298-02 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 480 spectra of 12 reference samples from the substance/substance group *Starch*. These samples are listed above in the [calibration samples](#) section.
- 70 906 spectra from a total of 1540 batches from further 371 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 546 spectra of 16 reference samples from the substance/substance group *Starch*.

| Supplier | Substance     | Batch      | Sample ID          | Spectra |
|----------|---------------|------------|--------------------|---------|
| Fagron   | Rice starch   | 9F02-N03   | 20038              | 76      |
| Caelo    | Corn starch   | 91955439   | 20181              | 50      |
| Fagron   | Wheat starch  | 10015905   | 20199              | 40      |
| Caelo    | Potato starch | 9352108    | 20244              | 50      |
| Caelo    | Wheat starch  | 14023203   | 21447 <sup>†</sup> | 20      |
| Caelo    | Corn starch   | 13154914   | 21827 <sup>†</sup> | 20      |
| Caelo    | Potato starch | 14033815   | 21965 <sup>†</sup> | 20      |
| Klenk    | Wheat starch  | 104A141114 | 21973 <sup>†</sup> | 20      |
| Caelo    | Wheat starch  | 15124707   | 22246 <sup>†</sup> | 20      |
| Caelo    | Potato starch | 161237     | 22449 <sup>†</sup> | 20      |
| Caelo    | Corn starch   | 161385     | 22450 <sup>†</sup> | 20      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.



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| Supplier | Substance     | Batch            | Sample ID | Spectra |
|----------|---------------|------------------|-----------|---------|
| Caelo    | Potato starch | 15062921         | 23189     | 40      |
| Caelo    | Corn starch   | 16138505         | 23217     | 40      |
| Fagron   | Rice starch   | 16B25-B01-327231 | 23219     | 30      |
| Caelo    | Wheat starch  | 15421507         | 23509     | 40      |
| Klenk    | Wheat starch  | 104A160512       | 23510     | 40      |

- 146 183 spectra from a total of 3178 batches from further 859 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 189 spectra from 98 *Apo-Ident* customers from 81 batches from the substance/substance group *Starch*.

| Supplier             | Substance     | Batch      | Spectra |
|----------------------|---------------|------------|---------|
| Caelo                | Rice starch   | 12238704   | 1       |
| Klenk                | Rice starch   | 64A130304  | 10      |
| Gutenberg-Apotheke   | Rice starch   | 12360216   | 1       |
| Caelo                | Rice starch   | 14011627   | 2       |
| VDL;3,03EUR;11.06.15 | Rice starch   | 14011630   | 1       |
| Caelo                | Rice starch   | P134/14    | 1       |
| Caelo                | Corn starch   | 15310902   | 2       |
| Klenk                | Corn starch   | 64A080218  | 7       |
| Caelo                | Corn starch   | 1179307    | 1       |
| Caelo                | Corn starch   | 12238705   | 2       |
| Caelo                | Corn starch   | 11179315   | 2       |
| Caelo                | Corn starch   | 12238715   | 3       |
| Klenk                | Wheat starch  | 104A120621 | 2       |
| Klenk                | Potato starch | 94A130304  | 3       |
| Klenk                | Potato starch | 94a170123  | 1       |
| Caelo                | Potato starch | 11301012   | 2       |
| Caelo                | Potato starch | 14033815   | 1       |
| Caelo                | Potato starch | 15062912   | 1       |
| Klenk                | Potato starch | 94A110512  | 1       |
| Bombastus            | Potato starch | 12214303   | 2       |
| Klenk                | Corn starch   | 64A130304  | 12      |
| Caelo                | Corn starch   | 64A130304  | 4       |
| Caelo                | Corn starch   | 15119011   | 5       |
| Caelo                | Corn starch   | 10061146   | 1       |
| Caelo                | Corn starch   | 11179307   | 1       |
| Caelo                | Corn starch   | 13154904   | 1       |
| Caelo                | Corn starch   | 15310903   | 2       |
| Caelo                | Corn starch   | 15310904   | 1       |
| Caelo                | Corn starch   | 15310909   | 2       |
| Caelo                | Corn starch   | 15310914   | 3       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| <b>Supplier</b> | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|-----------------|------------------|------------------|----------------|
| GEHE            | Corn starch      | 64A080218        | 2              |
| Klenk           | Rice starch      | 84A141114        | 3              |
| Caelo           | Rice starch      | 15118607         | 2              |
| Caelo           | Rice starch      | 15118611         | 1              |
| Caelo           | Rice starch      | 10177507         | 1              |
| Caelo           | Rice starch      | 10177515         | 1              |
| Caelo           | Rice starch      | 11186027         | 1              |
| Cael/Sanacorp   | Rice starch      | 16144501         | 2              |
| Caelo           | Rice starch      | 14025733         | 1              |
| Caelo           | Rice starch      | 16218002         | 1              |
| Klenk           | Rice starch      | 64A080218        | 3              |
| Klenk           | Rice starch      | 104A120621       | 4              |
| Caelo           | Rice starch      | 11186026         | 2              |
| Caelo           | Rice starch      | 12238714         | 2              |
| Caelo           | Rice starch      | 12238719         | 1              |
| Caelo           | Rice starch      | 13005905         | 2              |
| Caelo           | Rice starch      | 12166007         | 2              |
| Caelo           | Rice starch      | 200613K3         | 1              |
| Caelo           | Rice starch      | 13154904         | 3              |
| Klenk           | Rice starch      | 84A130304        | 1              |
| Klenk           | Rice starch      | 64a130304        | 1              |
| Caelo           | Rice starch      | 64A130304        | 1              |
| Klenk           | Rice starch      | 104A130304       | 7              |
| Klenk           | Rice starch      | 104A141114       | 3              |
| Caelo           | Rice starch      | 12068520         | 1              |
| Caelo           | Rice starch      | 104A141114       | 1              |
| Caelo           | Rice starch      | 13005908         | 1              |
| Caelo           | Rice starch      | 13089507         | 1              |
| Caelo           | Rice starch      | 13305103         | 3              |
| Caelo           | Rice starch      | 13305108         | 1              |
| Caelo           | Rice starch      | 14011612         | 2              |
| Caelo           | Rice starch      | 13305103         | 1              |
| Caelo           | Rice starch      | 14011621         | 1              |
| Noweda          | Rice starch      | 14011621         | 1              |
| Caelo           | Rice starch      | 14011630         | 2              |
| Noweda          | Rice starch      | 14023203         | 1              |
| Caelo           | Rice starch      | 14023203         | 3              |
| Caelo           | Rice starch      | 14025710         | 1              |
| Fagron          | Rice starch      | 14F18-B04-301616 | 1              |
| Caelo           | Rice starch      | 15119001         | 1              |
| Caelo           | Rice starch      | 15119011         | 1              |
| Caelo           | Rice starch      | 16101401         | 1              |
| Caelo           | Rice starch      | 2212M-01115      | 1              |
| Klenk           | Rice starch      | 94A100122        | 1              |
| Klenk           | Rice starch      | 94A120621        | 1              |
| Caelo           | Rice starch      | 104A120621       | 1              |
| Caelo           | Rice starch      | 9352108          | 1              |
| Caelo           | Rice starch      | 10061134         | 2              |
| Caelo           | Rice starch      | 11132406         | 1              |
| Caelo           | Rice starch      | 12214303         | 1              |
| Caelo           | Rice starch      | 12214307         | 1              |
| Fagron          | Rice starch      | 12L19-N06        | 1              |
| Caelo           | Rice starch      | 13154914         | 1              |
| Nachprüfung     | Rice starch      | 3709E01116       | 1              |
| Koisser         | Rice starch      | WE07032013       | 1              |
| Caelo           | Wheat starch     | 1114611          | 1              |
| Klenk           | Wheat starch     | 104a141114       | 1              |
| Klenk           | Wheat starch     | 104A141114       | 3              |
| Caelo           | Wheat starch     | 15124707         | 1              |
| Caelo           | Wheat starch     | 1512477          | 1              |

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| Supplier                    | Substance    | Batch      | Spectra |
|-----------------------------|--------------|------------|---------|
| Caelo                       | Wheat starch | 104A141114 | 1       |
| Klenk                       | Wheat starch | 104A160512 | 3       |
| Klenk                       | Wheat starch | 10A160512  | 1       |
| Klenk                       | Wheat starch | 104A101116 | 1       |
| Anzag 17.04.13 ek: 9,65EUR  | Wheat starch | 104A120621 | 2       |
| Caelo                       | Wheat starch | 10015911   | 1       |
| Caelo                       | Wheat starch | 11146011   | 1       |
| Caelo                       | Wheat starch | 11350907   | 3       |
| Caelo                       | Wheat starch | 11350911   | 4       |
| Fiebig 16.01.13 ek: 4,18EUR | Wheat starch | 11350911   | 1       |

- 69 444 spectra from 414 *Apo-Ident* customers from a total of 23 722 batches from a further 693 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Starch* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Starch* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 480           | 0              | 70 906        |
| <b>Type B</b> | 0              | 544           | 2              | 146 182       |
| <b>Type C</b> | 0              | 181           | 8              | 69 444        |

The substance/substance group *Starch* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.7500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.6337 % (> 99.0842 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 95.7672 % (> 94.1799 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20790     | 23220               | 5.95                         | 17.98                           |
| 20996     | 20996               | 0.00                         | 47.21                           |
| 21447     | 21447               | 0.00                         | 16.89                           |
| 21827     | 21447               | 5.42                         | 15.23                           |
| 21965     | 20996               | 5.90                         | 44.45                           |
| 21973     | 21447               | 3.73                         | 18.80                           |
| 22246     | 22450               | 6.53                         | 17.95                           |
| 22449     | 22449               | 0.00                         | 44.38                           |
| 22450     | 22450               | 0.00                         | 19.69                           |
| 22585     | 22450               | 5.74                         | 18.36                           |
| 22642     | 22642               | 0.00                         | 12.12                           |
| 23220     | 23220               | 0.00                         | 15.76                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Stearic acid 50**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20869-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Stearic acid 50; Acidum stearicum; Acidum stearinicum

### Special notes

When selecting the *Stearic acid 50* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Stearic acid 50*:

| Supplier | Substance       | Batch    | Sample ID | Spectra | Certificate        |
|----------|-----------------|----------|-----------|---------|--------------------|
| Caelo    | Stearic acid 50 | 12241910 | 20869     | 40      | AR-15-FG-007284-01 |
| Caelo    | Stearic acid 50 | 14359310 | 21928     | 40      | AR-16-FG-004044-01 |
| Caelo    | Stearic acid 50 | 14359314 | 22274     | 40      | 20150126           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Stearic acid 50*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 6 reference samples from the substance/substance group *Stearic acid 50*.

| Supplier | Substance       | Batch    | Sample ID          | Spectra |
|----------|-----------------|----------|--------------------|---------|
| Caelo    | Stearic acid 50 | 14359310 | 21793              | 60      |
| Caelo    | Stearic acid 50 | 14359310 | 21928 <sup>†</sup> | 20      |
| Caelo    | Stearic acid 50 | 14359314 | 22274 <sup>†</sup> | 20      |
| Caelo    | Stearic acid 50 | 163469   | 23032              | 40      |
| Caelo    | Stearic acid 50 | 170810   | 23294              | 40      |
| Caelo    | Stearic acid 50 | 170810   | 23667              | 40      |

- 146 509 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 26 spectra from 18 *Apo-Ident* customers from 14 batches from the substance/substance group *Stearic acid 50*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                 | Substance       | Batch    | Spectra |
|--------------------------|-----------------|----------|---------|
| Caelo                    | Stearic acid 50 | 10176203 | 1       |
| Caelo                    | Stearic acid 50 | 12241915 | 5       |
| Caelo                    | Stearic acid 50 | 12241911 | 2       |
| Caelo                    | Stearic acid 50 | 1224     | 1       |
| Caelo                    | Stearic acid 50 | 12241914 | 1       |
| Phoenix                  | Stearic acid 50 | 12241915 | 1       |
| Caelo                    | Stearic acid 50 | 12241930 | 3       |
| Caesar & Loretz          | Stearic acid 50 | 14359310 | 1       |
| Phönix                   | Stearic acid 50 | 1224915  | 1       |
| Caelo                    | Stearic acid 50 | 14359314 | 3       |
| Caelo                    | Stearic acid 50 | 16096301 | 1       |
| Caelo                    | Stearic acid 50 | 11103706 | 1       |
| Caesar&Loretz GmbH/Anzag | Stearic acid 50 | 11308505 | 1       |
| Caelo                    | Stearic acid 50 | 11308505 | 1       |
| Caelo                    | Stearic acid 50 | 16096311 | 1       |
| Caelo                    | Stearic acid 50 | 11308514 | 2       |

- 69 607 spectra from 414 *Apo-Ident* customers from a total of 23 787 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Stearic acid 50* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Stearic acid 50* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 220           | 0              | 146 509       |
| <b>Type C</b> | 0              | 26            | 0              | 69 607        |

The substance/substance group *Stearic acid 50* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.2727 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 76.9231 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20869     | 20869               | 0.00                         | 63.81                           |
| 21928     | 21928               | 0.00                         | 61.98                           |
| 22274     | 20869               | 3.98                         | 61.35                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sucrose**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20372-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sucrose; Saccharum

### Special notes

When selecting the *Sucrose* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sucrose*:

| Supplier | Substance | Batch    | Sample ID | Spectra | Certificate |
|----------|-----------|----------|-----------|---------|-------------|
| Caelo    | Sucrose   | 13352909 | 21484     | 40      | 1410501     |
| Caelo    | Sucrose   | 14340003 | 21736     | 40      | 20141114    |
| Caelo    | Sucrose   | 163286   | 23057     | 40      | 20161219*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Sucrose*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 340 spectra of 9 reference samples from the substance/substance group *Sucrose*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Fagron   | Sucrose   | 11B02-N12  | 20216              | 40      |
| Caelo    | Sucrose   | 1901208731 | 20372              | 40      |
| Caelo    | Sucrose   | 12146801   | 20909              | 40      |
| Caelo    | Sucrose   | 14340003   | 21736 <sup>†</sup> | 20      |
| Caelo    | Sucrose   | 161999     | 22615              | 40      |
| Caelo    | Sucrose   | 162060     | 22643              | 40      |
| Caelo    | Sucrose   | 163081     | 23058              | 40      |
| Caelo    | Sucrose   | 171066     | 23297              | 40      |
| Caelo    | Sucrose   | 172133     | 23666              | 40      |

- 146 389 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 259 spectra from 97 *Apo-Ident* customers from 129 batches from the substance/substance group *Sucrose*.

| Supplier             | Substance | Batch      | Spectra |
|----------------------|-----------|------------|---------|
| Werner               | Sucrose   | 1901208731 | 2       |
| Caelo                | Sucrose   |            | 2       |
| Caelo                | Sucrose   | 12241803   | 2       |
| Caelo                | Sucrose   | 13031409   | 3       |
| pharm-a-speres       | Sucrose   | 8731003    | 1       |
| Caelo                | Sucrose   | 11246306   | 1       |
| Caelo                | Sucrose   | 13031405   | 5       |
| Phönix 13.05.2013    | Sucrose   | 1256433    | 1       |
| Caelo                | Sucrose   | 13352902   | 14      |
| Penny                | Sucrose   | L12513800  | 3       |
| Caelo                | Sucrose   | 14197302   | 4       |
| Caelo                | Sucrose   | 15028802   | 3       |
| Fagron               | Sucrose   | 1011208731 | 2       |
| Soldan               | Sucrose   | 232027     | 1       |
| Noweda               | Sucrose   | 10179620   | 1       |
| Caelo                | Sucrose   | 11246307   | 1       |
| Fagron               | Sucrose   | 11/16-N01  | 1       |
| Fagron               | Sucrose   | 11/16-N01  | 1       |
| Caelo                | Sucrose   | 11246313   | 2       |
| Caelo                | Sucrose   | 12107805   | 1       |
| Fagron               | Sucrose   | 11I16-N01  | 1       |
| Fagron               | Sucrose   | 11B02-N12  | 1       |
| Fagron               | Sucrose   | 11L09-N16  | 2       |
| Noweda               | Sucrose   | 12241801   | 1       |
| Caelo                | Sucrose   | 12107806   | 1       |
| Fagron               | Sucrose   | 11E19-N04  | 1       |
| Caelo                | Sucrose   | 12241801   | 1       |
| Noweda               | Sucrose   | 12241803   | 1       |
| Caelo                | Sucrose   | 12241808   | 7       |
| Caelo                | Sucrose   | 12241804   | 4       |
| Caelo                | Sucrose   | 12241816   | 2       |
| Euro OTC             | Sucrose   | 12241808   | 1       |
| Caelo                | Sucrose   | 12241817   | 3       |
| Caelo                | Sucrose   | 12280309   | 1       |
| Haushalt             | Sucrose   | 123456     | 1       |
| Fagron               | Sucrose   | 12-E03-M01 | 1       |
| Fagron               | Sucrose   | 12E29-N04  | 1       |
| Caelo                | Sucrose   | 130031417  | 1       |
| Fagron               | Sucrose   | 130100R    | 1       |
| Caelo                | Sucrose   | 13031406   | 2       |
| Caelo                | Sucrose   | 13031410   | 4       |
| Caelo                | Sucrose   | 13031414   | 3       |
| Caelo                | Sucrose   | 13031417   | 2       |
| Caelo                | Sucrose   | 13352901   | 3       |
| Caelo                | Sucrose   | 13352908   | 1       |
| Caelo                | Sucrose   | 13352909   | 5       |
| Caelo                | Sucrose   | 13352905   | 1       |
| Caelo                | Sucrose   | 13352911   | 1       |
| Infectopharm/Phoenix | Sucrose   | 13352909   | 1       |
| Caelo                | Sucrose   | 13352916   | 3       |
| Noweda               | Sucrose   | 13352920   | 2       |
| Caelo                | Sucrose   | 13352920   | 4       |
| Fagron               | Sucrose   | 13A07-N03  | 1       |
| Fagron               | Sucrose   | 13D29-N08  | 1       |
| Fagron               | Sucrose   | 13G03-N16  | 1       |
| Fagron               | Sucrose   | 13I30-N05  | 1       |

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| <b>Supplier</b> | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|-----------------|------------------|------------------|----------------|
| Caelo           | Sucrose          | 1352920          | 1              |
| Fagron          | Sucrose          | 13J11-N01        | 1              |
| Caelo           | Sucrose          | 14197301         | 5              |
| Fagron          | Sucrose          | 13K18-B33-288225 | 1              |
| Caelo           | Sucrose          | 14340003         | 2              |
| Caelo           | Sucrose          | 14197313         | 1              |
| Caelo           | Sucrose          | 14340004         | 4              |
| Caelo           | Sucrose          | 14340005         | 1              |
| Caelo           | Sucrose          | 14340006         | 1              |
| Caelo           | Sucrose          | 14340008         | 2              |
| Caelo           | Sucrose          | 14340009         | 2              |
| Caelo           | Sucrose          | 15028801         | 13             |
| Caelo           | Sucrose          | 15182804         | 11             |
| Caelo           | Sucrose          | 15156008         | 1              |
| Jenne           | Sucrose          | 15182804         | 1              |
| Caelo           | Sucrose          | 15182805         | 1              |
| Caelo           | Sucrose          | 15446002         | 4              |
| AHD             | Sucrose          | 15182805         | 1              |
| Phönix          | Sucrose          | 15446002         | 1              |
| Fagron          | Sucrose          | 15446002         | 1              |
| Caelo           | Sucrose          | 15446003         | 2              |
| Caelo           | Sucrose          | 16049907         | 3              |
| Caelo           | Sucrose          | 16206102         | 5              |
| Caelo           | Sucrose          | 15446007         | 1              |
| Caelo           | Sucrose          | 16206103         | 1              |
| Caelo           | Sucrose          | 16328603         | 1              |
| Caelo           | Sucrose          | 16328605         | 3              |
| Fagron          | Sucrose          | 18082014D        | 1              |
| Caelo           | Sucrose          | 20011401         | 1              |
| Caelo           | Sucrose          | 16328606         | 1              |
| Caelo           | Sucrose          | 20031515         | 1              |
| Penny Markt     | Sucrose          | 201L113530100    | 3              |
| Fagron          | Sucrose          | 2102308731       | 1              |
| Caelo           | Sucrose          | 24061502         | 1              |
| Caelo           | Sucrose          | 23121-02207      | 1              |
| Caelo           | Sucrose          | 28081308         | 1              |
| Caelo           | Sucrose          | 28041504         | 1              |
| Caelo           | Sucrose          | 29081502         | 1              |
| Fagron          | Sucrose          | 5112I-02207      | 1              |
| Pfeifer/Langen  | Sucrose          | L03144N          | 1              |
| Sanacorp        | Sucrose          | AKD5             | 1              |
| Penny Markt     | Sucrose          | L120404100       | 3              |
| Penny Markt     | Sucrose          | L120325600       | 2              |
| Penny Markt     | Sucrose          | L120628000       | 3              |
| Kaufland        | Sucrose          | L24494           | 2              |
| Kaufland        | Sucrose          | L24475           | 1              |
| Fagron          | Sucrose          | 11/20-N05        | 1              |
| Fagron          | Sucrose          | 5071201          | 1              |
| Spagyra         | Sucrose          | 12082320717      | 1              |
| Spagyra         | Sucrose          | 12091120645      | 1              |
| Spagyra         | Sucrose          | 1210222892       | 1              |
| Fagron          | Sucrose          | 12G26-N01        | 3              |
| Spagyra         | Sucrose          | 12103020975      | 1              |
| Spagyra         | Sucrose          | 13012920302      | 1              |
| Spagyra         | Sucrose          | 13030621373      | 1              |
| Spagyra         | Sucrose          | 13020620240      | 1              |
| Spagyra         | Sucrose          | 13040921424      | 1              |
| Spagyra         | Sucrose          | 13040921431      | 1              |
| Spagyra         | Sucrose          | 13040921427      | 1              |
| Spagyra         | Sucrose          | 13041920154      | 1              |

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| Supplier        | Substance | Batch       | Spectra |
|-----------------|-----------|-------------|---------|
| Spagyra         | Sucrose   | 13050621773 | 2       |
| Spagyra         | Sucrose   | 13040921430 | 1       |
| Spagyra         | Sucrose   | 13051520939 | 1       |
| Spagyra         | Sucrose   | 13041920152 | 1       |
| Spagyra         | Sucrose   | 13051520941 | 1       |
| Spagyra         | Sucrose   | 13061020526 | 1       |
| Spagyra         | Sucrose   | 13061020524 | 1       |
| Spagyra         | Sucrose   | 13061020528 | 1       |
| Spagyra         | Sucrose   | 13061020525 | 1       |
| Caelo           | Sucrose   | 13063907    | 1       |
| Spagyra         | Sucrose   | 13070420936 | 1       |
| Spagyra         | Sucrose   | 13061020529 | 1       |
| Spagyra         | Sucrose   | 13061220385 | 1       |
| Spagyra         | Sucrose   | 13070420938 | 1       |
| Spagyra         | Sucrose   | 13072620834 | 1       |
| Spagyra         | Sucrose   | 13070420937 | 1       |
| Fagron          | Sucrose   | 13G04-N01   | 1       |
| Gehe 02.07.2013 | Sucrose   | 1911208731  | 1       |
| Staufen-Pharma  | Sucrose   | 161112      | 2       |
| Soldan          | Sucrose   |             | 1       |
| Soldan          | Sucrose   | 243983      | 1       |
| Penny Markt     | Sucrose   | L120612100  | 3       |

- 69 374 spectra from 414 *Apo-Ident* customers from a total of 23 675 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sucrose* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sucrose* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 258           | 82             | 146 389       |
| <b>Type C</b> | 0              | 216           | 43             | 69 374        |

The substance/substance group *Sucrose* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 75.8824 % (> 75.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 83.3977 % (> 82.2394 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21484     | 21484               | 0.00                         | 51.56                           |
| 21736     | 21484               | 1.97                         | 51.14                           |
| 23057     | 23057               | 0.00                         | 49.73                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sulfacetamide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20695-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sulfacetamide; Sulfacetamidum

### Special notes

When selecting the *Sulfacetamide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sulfacetamide*:

| Supplier | Substance     | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------|------------|-----------|---------|-------------|
| Caelo    | Sulfacetamide | 11085910   | 20695     | 40      | 1402651     |
| Euro OTC | Sulfacetamide | 1312012-01 | 21633     | 40      | 20140117    |
| Euro OTC | Sulfacetamide | 1509018    | 21902     | 40      | 20150929*   |
| Caelo    | Sulfacetamide | 15445901   | 23251     | 40      | 20160126    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Sulfacetamide*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 160 spectra of 5 reference samples from the substance/substance group *Sulfacetamide*.

| Supplier | Substance     | Batch      | Sample ID          | Spectra |
|----------|---------------|------------|--------------------|---------|
| Caelo    | Sulfacetamide | 10145802   | 20140              | 40      |
| Euro OTC | Sulfacetamide | 1312012-01 | 21633 <sup>†</sup> | 20      |
| Euro OTC | Sulfacetamide | 1509018    | 21902 <sup>†</sup> | 20      |
| Euro OTC | Sulfacetamide | 1702006    | 23157              | 40      |
| Caelo    | Sulfacetamide | 15445901   | 23456              | 40      |

- 146 569 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 53 spectra from 21 *Apo-Ident* customers from 18 batches from the substance/substance group *Sulfacetamide*.

| Supplier              | Substance     | Batch      | Spectra |
|-----------------------|---------------|------------|---------|
| Euro OTC              | Sulfacetamide | 1312012-01 | 4       |
| Gehe                  | Sulfacetamide | 1312012-01 | 2       |
| EuRho/Phönix          | Sulfacetamide | 131201202  | 1       |
| Euro OTC              | Sulfacetamide | 1312012-02 | 2       |
| Phönix Gotha          | Sulfacetamide | 1312012-02 | 1       |
| Euro OTC              | Sulfacetamide | 1509018-01 | 4       |
| Euro OTC              | Sulfacetamide | 1509018-02 | 3       |
| Industrias GmbH / Ph  | Sulfacetamide | 64518      | 1       |
| Caelo                 | Sulfacetamide | 10145802   | 1       |
| Caelo                 | Sulfacetamide | 10145811   | 1       |
| Phönix Gotha          | Sulfacetamide | 10145811   | 2       |
| Klenk                 | Sulfacetamide | 11085904   | 1       |
| Phoenix am 15.06.2012 | Sulfacetamide | 11085904   | 1       |
| Gehe                  | Sulfacetamide | 11085904   | 1       |
| Phönix Gotha          | Sulfacetamide | 11085909   | 1       |
| Caelo                 | Sulfacetamide | 11085909   | 1       |
| Phönix                | Sulfacetamide | 11085910   | 1       |
| Caelo                 | Sulfacetamide | 11085911   | 3       |
| Phönix Gotha          | Sulfacetamide | 11085911   | 1       |
| Caelo                 | Sulfacetamide | 11085912   | 3       |
| AHC 12.08.13 EK9,31   | Sulfacetamide | 11085912   | 1       |
| Caelo                 | Sulfacetamide | 11085914   | 2       |
| Gehe                  | Sulfacetamide | 1112032-01 | 5       |
| Euro OTC              | Sulfacetamide | 1112032-02 | 5       |
| Euro OTC              | Sulfacetamide | 1112032-01 | 3       |
| Caelo                 | Sulfacetamide | 11095912   | 1       |
| Caelo                 | Sulfacetamide | 11085913   | 1       |

- 69 580 spectra from 414 *Apo-Ident* customers from a total of 23 783 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sulfacetamide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sulfacetamide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 150           | 10             | 146 569       |
| <b>Type C</b> | 0              | 51            | 2              | 69 580        |

The substance/substance group *Sulfacetamide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 93.7500 % (> 91.8750 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 96.2264 % (> 90.5660 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20695     | 20695               | 0.00                         | 59.38                           |
| 21633     | 21902               | 4.91                         | 58.47                           |
| 21902     | 21902               | 0.00                         | 52.36                           |
| 23251     | 21902               | 7.78                         | 68.60                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sulfadiazine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20753-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sulfadiazine; Sulfadiazinum

### Special notes

When selecting the *Sulfadiazine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sulfadiazine*:

| Supplier | Substance    | Batch    | Sample ID | Spectra | Certificate |
|----------|--------------|----------|-----------|---------|-------------|
| Caelo    | Sulfadiazine | 12164101 | 20753     | 40      | 1402053     |
| Caelo    | Sulfadiazine | 13150011 | 21744     | 40      | 20130708    |
| Caelo    | Sulfadiazine | 17056602 | 23447     | 40      | 20170330    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Sulfadiazine*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Sulfadiazine*.

| Supplier | Substance    | Batch    | Sample ID          | Spectra |
|----------|--------------|----------|--------------------|---------|
| Caelo    | Sulfadiazine | 13150011 | 21744 <sup>†</sup> | 20      |
| Caelo    | Sulfadiazine | 170566   | 23319              | 40      |
| Caelo    | Sulfadiazine | 17056602 | 23374              | 40      |
| Caelo    | Sulfadiazine | 172222   | 23630              | 40      |

- 146 589 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 2 spectra from 2 *Apo-Ident* customers from 2 batches from the substance/substance group *Sulfadiazine*.

| Supplier | Substance    | Batch    | Spectra |
|----------|--------------|----------|---------|
| Caelo    | Sulfadiazine | 11194204 | 1       |
| Caelo    | Sulfadiazine | 13150004 | 1       |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sulfadiazine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sulfadiazine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 140           | 0              | 146 589       |
| <b>Type C</b> | 0              | 2             | 0              | 69 631        |

The substance/substance group *Sulfadiazine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.7143 %) |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20753     | 20753               | 0.00                         | 92.86                           |
| 21744     | 20753               | 2.50                         | 93.14                           |
| 23447     | 20753               | 7.35                         | 90.83                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe

mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Sulfogaiacol hydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20327-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Sulfogaiacol hydrate; Kalii sulfuajacolicum; Sulfoguaiacolum hydricum

### Special notes

When selecting the *Sulfogaiacol hydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Sulfogaiacol hydrate*:

| Supplier    | Substance           | Batch         | Sample ID | Spectra | Certificate        |
|-------------|---------------------|---------------|-----------|---------|--------------------|
| Caelo       | Sulfogaiacol hyd... | 13405805      | 21696     | 30      | 20140108           |
| Gatt-Koller | Sulfogaiacol hyd... | 1156/04152115 | 21843     | 40      | 20150410           |
| Gatt-Koller | Sulfogaiacol hyd... | 4543/01170317 | 23113     | 40      | AR-17-FG-012520-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 110 spectra of 3 reference samples from the substance/substance group *Sulfogaiacol hydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 276 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 167 spectra of 6 reference samples from the substance/substance group *Sulfogaiacol hydrate*.

| Supplier    | Substance            | Batch         | Sample ID          | Spectra |
|-------------|----------------------|---------------|--------------------|---------|
| Caelo       | Sulfogaiacol hydrate | 10353605      | 20327              | 40      |
| Caelo       | Sulfogaiacol hydrate | 13405805      | 21696 <sup>†</sup> | 15      |
| Gatt-Koller | Sulfogaiacol hydrate | 1156/04152115 | 21843 <sup>†</sup> | 20      |
| Caelo       | Sulfogaiacol hydrate | 170919        | 23300              | 40      |
| Caelo       | Sulfogaiacol hydrate | 170919        | 23306              | 40      |
| Caelo       | Sulfogaiacol hydrate | 15343912      | not required       | 12      |

- 146 562 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Sulfogaiacol hydrate*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Sulfogaiacol hydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Sulfogaiacol hydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 110           | 0              | 71 276        |
| <b>Type B</b> | 0              | 155           | 12             | 146 562       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Sulfogaiacol hydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 94.5455 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 92.8144 % (> 91.0180 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21696     | 23113               | 8.73                         | 76.77                           |
| 21843     | 23113               | 7.67                         | 79.31                           |
| 23113     | 23113               | 0.00                         | 83.31                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR

bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **SyrSpend<sup>®</sup> SF / pH4**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 22494-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

SyrSpend<sup>®</sup> SF / pH4; SyrSpend<sup>®</sup> SF Alka; SyrSpend<sup>®</sup> SF pH4

### Special notes

When selecting the *SyrSpend<sup>®</sup> SF / pH4* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *SyrSpend<sup>®</sup> SF / pH4*:

| Supplier | Substance                     | Batch            | Sample ID | Spectra | Certificate |
|----------|-------------------------------|------------------|-----------|---------|-------------|
| Fagron   | SyrSpend <sup>®</sup> SF Alka | 15H11-B04-311722 | 22494     | 40      | 1608351     |
| Fagron   | SyrSpend <sup>®</sup> SF pH4  | 15A26-B04-311720 | 22496     | 40      | 1608352     |
| Fagron   | SyrSpend <sup>®</sup> SF Alka | 15H11-B04-311722 | 22718     | 20      | 1701054     |
| Fagron   | SyrSpend <sup>®</sup> SF pH4  | 15A26-B04-305667 | 22719     | 40      | 1701055     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 140 spectra of 4 reference samples from the substance/substance group *SyrSpend<sup>®</sup> SF / pH4*. These samples are listed above in the [calibration samples](#) section.
- 71 246 spectra from a total of 1549 batches from further 373 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 260 spectra of 7 reference samples from the substance/substance group *SyrSpend<sup>®</sup> SF / pH4*.

| Supplier | Substance                     | Batch            | Sample ID          | Spectra |
|----------|-------------------------------|------------------|--------------------|---------|
| Fagron   | SyrSpend <sup>®</sup> SF Alka | 15H11-B04-311722 | 22495              | 40      |
| Fagron   | SyrSpend <sup>®</sup> SF pH4  | 15A26-B04-311720 | 22497              | 40      |
| Fagron   | SyrSpend <sup>®</sup> SF Alka | 15H11-B04-311722 | 22718 <sup>†</sup> | 20      |
| Fagron   | SyrSpend <sup>®</sup> SF Alka | 17D11-B04-332593 | 23448              | 40      |
| Fagron   | SyrSpend <sup>®</sup> SF Alka | 17D11-B04-332593 | 23449              | 40      |
| Fagron   | SyrSpend <sup>®</sup> SF pH4  | 15H13-B03-314611 | 23450              | 40      |
| Fagron   | SyrSpend <sup>®</sup> SF pH4  | 15H13-B03-314611 | 23451              | 40      |

- 146 469 spectra from a total of 3190 batches from further 861 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 2 spectra from 2 *Apo-Ident* customers from 2 batches from the substance/substance group *SyrSpend<sup>®</sup> SF / pH4*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance                     | Batch            | Spectra |
|----------|-------------------------------|------------------|---------|
| Fagron   | SyrSpend <sup>®</sup> SF Alka | 17D11-B04-332593 | 1       |
| Fagron   | SyrSpend <sup>®</sup> SF Alka | 17D11-bo4-332593 | 1       |

- 69 631 spectra from 414 *Apo-Ident* customers from a total of 23 799 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *SyrSpend<sup>®</sup> SF / pH4* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *SyrSpend<sup>®</sup> SF / pH4* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 140           | 0              | 71 246        |
| <b>Type B</b> | 0              | 151           | 109            | 146 468       |
| <b>Type C</b> | 0              | 0             | 2              | 69 631        |

The substance/substance group *SyrSpend<sup>®</sup> SF / pH4* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.7143 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 58.0769 % (> 56.9231 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8819 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22494     | 22494               | 0.00                         | 34.84                           |
| 22496     | 22496               | 0.00                         | 20.30                           |
| 22718     | 22718               | 0.00                         | 11.83                           |
| 22719     | 22719               | 0.00                         | 12.04                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tannin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20018-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tannin; Acidum tannicum; Tanninum

### Special notes

When selecting the *Tannin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tannin*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------|------------------|-----------|---------|--------------------|
| Caelo    | Tannin    | 12336016         | 21608     | 40      | 20121127           |
| Fagron   | Tannin    | 13H30-B03-287645 | 21653     | 40      | 1711482            |
| Fagron   | Tannin    | 16D08-B04-328410 | 23211     | 40      | AR-17-FG-015963-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Tannin*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 6 reference samples from the substance/substance group *Tannin*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Caelo    | Tannin    | 81318508         | 20018              | 80      |
| Caelo    | Tannin    | 12336016         | 21608 <sup>†</sup> | 20      |
| Fagron   | Tannin    | 13H30-B03-287645 | 21653 <sup>†</sup> | 20      |
| Caelo    | Tannin    | 16074504         | 23205              | 40      |
| Fagron   | Tannin    | 16D08-B04-328410 | 23501              | 40      |
| Caelo    | Tannin    | 172092           | 23631              | 40      |

- 146 489 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 241 spectra from 140 *Apo-Ident* customers from 85 batches from the substance/substance group *Tannin*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier            | Substance | Batch            | Spectra |
|---------------------|-----------|------------------|---------|
| Caelo               | Tannin    | 12336011         | 4       |
| Caelo               | Tannin    | 14031913         | 3       |
| Caelo               | Tannin    | 11302306         | 1       |
| Fagron              | Tannin    | 2212M-01052      | 1       |
| Caelo               | Tannin    | 11302307         | 7       |
| Herbasinica         | Tannin    | 12171101         | 2       |
| Fagron              | Tannin    | 12H14N05         | 1       |
| Fagron              | Tannin    | 12H14-N05        | 6       |
| Caelo               | Tannin    | 2211Q-01052      | 1       |
| A.H.D.              | Tannin    | 13E27-N08        | 1       |
| Caelo               | Tannin    | 12336016         | 10      |
| Sanacorp            | Tannin    |                  | 1       |
| Caelo               | Tannin    | 9128601          | 1       |
| Caelo               | Tannin    | 12171101         | 5       |
| Caelo               | Tannin    | 12171106         | 9       |
| Caelo               | Tannin    | 12336009         | 11      |
| Caelo               | Tannin    | 14031903         | 3       |
| Hirsch              | Tannin    | 1811209          | 1       |
| Caelo               | Tannin    | 9128608          | 1       |
| Caelo               | Tannin    | 10019007         | 2       |
| Fagron              | Tannin    | 1014A-01052      | 1       |
| Phönix              | Tannin    | 10313107Retest   | 1       |
| Caelo               | Tannin    | 10315107         | 3       |
| Caelo               | Tannin    | 10315110         | 2       |
| Phönix              | Tannin    | 10315110         | 1       |
| Caesar/Lorenz       | Tannin    | 11302307         | 1       |
| Fagron              | Tannin    | 11C09-N05        | 1       |
| Noweda              | Tannin    | 11G01-N08        | 1       |
| Anzag               | Tannin    | 12171101         | 1       |
| Sanacorp            | Tannin    | 12171102         | 1       |
| Caelo               | Tannin    | 12171102         | 1       |
| Caelo               | Tannin    | 12171103         | 2       |
| Gehe                | Tannin    | 12171106         | 1       |
| GEHE                | Tannin    | 12171106         | 1       |
| Caelo               | Tannin    | 12171110         | 2       |
| Caelo               | Tannin    | 12301515         | 1       |
| Caelo               | Tannin    | 12336001         | 13      |
| Alliance Healthcare | Tannin    | 12336001         | 1       |
| Gehe                | Tannin    | 12336001         | 1       |
| Caelo               | Tannin    | 12336005         | 2       |
| Caelo               | Tannin    | 12336007         | 2       |
| Sanacorp            | Tannin    | 12336011         | 1       |
| Caelo               | Tannin    | 12336013         | 5       |
| Phoenix             | Tannin    | 12336013         | 1       |
| Caelo               | Tannin    | 12336014         | 6       |
| Sanacorp            | Tannin    | 12336014         | 1       |
| Gehe                | Tannin    | 12336016         | 2       |
| Caelo               | Tannin    | 1236001          | 1       |
| Anzag, 24.10.2012   | Tannin    | 12A27-N01        | 1       |
| Fagron              | Tannin    | 12E21-N04        | 5       |
| Fagron              | Tannin    | 12A27-N01        | 1       |
| Gehe                | Tannin    | 12H14-N05        | 1       |
| Fagron              | Tannin    | 13B28-N08        | 1       |
| Fagron              | Tannin    | 13H30-B03-287645 | 2       |
| Caelo               | Tannin    | 13031401         | 1       |
| Fagron              | Tannin    | 13H30-B03287645  | 1       |
| Caelo               | Tannin    | 13E27-N08        | 1       |
| Caelo               | Tannin    | 14031901         | 2       |
| Caelo               | Tannin    | 14031905         | 5       |
| Sanacorp            | Tannin    | 14031912         | 1       |

*continued on the next page*

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| Supplier                | Substance | Batch            | Spectra |
|-------------------------|-----------|------------------|---------|
| Caelo                   | Tannin    | 14031912         | 3       |
| Caelo                   | Tannin    | 14031915         | 2       |
| Caelo                   | Tannin    | 14031918         | 4       |
| Caelo                   | Tannin    | 14031919         | 6       |
| Caelo                   | Tannin    | 14031920         | 1       |
| Fagron                  | Tannin    | 14A07-B01-293468 | 5       |
| Fagron                  | Tannin    | 14E07-B03-298480 | 2       |
| phönix                  | Tannin    | 14E07-B03-293744 | 1       |
| Fagron                  | Tannin    | 14e07-b03-298480 | 1       |
| Fagron                  | Tannin    | 14J06-B04        | 1       |
| Fagron                  | Tannin    | 14J06-B04-0858   | 1       |
| Fagron                  | Tannin    | 14J06-B04-299398 | 2       |
| Fagron                  | Tannin    | 14K17-B08        | 1       |
| Fagron                  | Tannin    | 14K17-B08-306993 | 1       |
| Fagron                  | Tannin    | 14J06B04299398   | 1       |
| Caelo                   | Tannin    | 15091504         | 3       |
| phönix                  | Tannin    | 15/AKD65         | 1       |
| Caelo                   | Tannin    | 15091506         | 1       |
| Caelo                   | Tannin    | 15091503         | 1       |
| Caleo/Phoenix           | Tannin    | 14K17-B08-306993 | 1       |
| Ebert u. Jacobi 16.0... | Tannin    | 15091509         | 1       |
| Caelo                   | Tannin    | 15091509         | 7       |
| Caelo                   | Tannin    | 15091512         | 1       |
| Caelo                   | Tannin    | 15091515         | 4       |
| Caelo                   | Tannin    | 1509503          | 1       |
| Caelo                   | Tannin    | 15243801         | 10      |
| Caelo                   | Tannin    | 15243802         | 3       |
| Caelo                   | Tannin    | 15F23-B01-326357 | 1       |
| Fagron                  | Tannin    | 160300029        | 2       |
| Fagron                  | Tannin    | 160300146        | 2       |
| Fagron                  | Tannin    | 160300069        | 1       |
| Caelo                   | Tannin    | 16074504         | 4       |
| Fagron                  | Tannin    | 160300178B       | 1       |
| Gehe                    | Tannin    | 16074504         | 1       |
| Caelo                   | Tannin    | 16074505         | 1       |
| Caelo                   | Tannin    | 28011502         | 1       |
| Fagron                  | Tannin    | 16D08-B04        | 1       |
| Caelo                   | Tannin    | 21101305         | 1       |
| Gatt-Koller / Phoenix   | Tannin    | 333508134613     | 2       |
| Gatt-Koller / Phoenix   | Tannin    | 3335/08134613    | 1       |
| Synopharm/Anzag         | Tannin    | 3411I-01052      | 1       |
| Caelo                   | Tannin    | 4413I1052        | 1       |
| Nachprüfung             | Tannin    | 5210A-01052      | 1       |
| Caelo                   | Tannin    |                  | 1       |
| Caelo                   | Tannin    | 1524308          | 1       |
| Fagron                  | Tannin    | 13E27-N08        | 1       |

- 69 392 spectra from 414 *Apo-Ident* customers from a total of 23 719 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tannin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all

relevant spectra of the various substances were compared with *Tannin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 207           | 33             | 146 489       |
| <b>Type C</b> | 0              | 226           | 15             | 69 392        |

The substance/substance group *Tannin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 86.2500 % (> 85.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 93.7759 % (> 92.5311 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21608     | 21653               | 14.49                        | 51.14                           |
| 21653     | 21653               | 0.00                         | 51.88                           |
| 23211     | 23211               | 0.00                         | 50.39                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

IdentModul 1.3-2018-01

Validated substance/substance group **Tartaric acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20014-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

## Relevant substance names

Tartaric acid; Acidum tartaricum

## Special notes

When selecting the *Tartaric acid* substance/substance group, the following information is displayed to the user:

*no information*

## Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

## Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

## Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tartaric acid*:

| Supplier | Substance     | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------|------------------|-----------|---------|-------------|
| Caelo    | Tartaric acid | 15130201         | 22383     | 40      | 20150416    |
| Caelo    | Tartaric acid | 15164001         | 22384     | 40      | 1704461     |
| Fagron   | Tartaric acid | 13I25-B01-294093 | 22391     | 40      | 1711509     |
| Fagron   | Tartaric acid | 14G07-B02-308554 | 22501     | 40      | 20140827    |
| Caelo    | Tartaric acid | 161468           | 22613     | 40      | 20160607*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Tartaric acid*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 270 spectra of 8 reference samples from the substance/substance group *Tartaric acid*.

| Supplier | Substance     | Batch            | Sample ID          | Spectra |
|----------|---------------|------------------|--------------------|---------|
| Caelo    | Tartaric acid | 90800249         | 20014              | 30      |
| Caelo    | Tartaric acid | 10199711         | 20493              | 40      |
| Caelo    | Tartaric acid | 12044101         | 20494              | 40      |
| Caelo    | Tartaric acid | 13217803         | 21457              | 60      |
| Caelo    | Tartaric acid | 15130201         | 22383 <sup>†</sup> | 20      |
| Caelo    | Tartaric acid | 15164001         | 22384 <sup>†</sup> | 20      |
| Fagron   | Tartaric acid | 13I25-B01-294093 | 22391 <sup>†</sup> | 20      |
| Fagron   | Tartaric acid | 14G07-B02-322976 | 23527              | 40      |

- 146 459 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 181 spectra from 91 *Apo-Ident* customers from 106 batches from the substance/substance group *Tartaric acid*.

| Supplier                | Substance     | Batch             | Spectra |
|-------------------------|---------------|-------------------|---------|
| Fischar/Phönix          | Tartaric acid | 704021            | 1       |
| Beiersdorf AG           | Tartaric acid | 11G19-N08         | 1       |
| Fagron                  | Tartaric acid | 13B15-N01         | 6       |
| VDL; 16.7.15; 4,59EUR   | Tartaric acid | 14186213          | 1       |
| Fagron                  | Tartaric acid | 12F18-No2         | 1       |
| Fagron                  | Tartaric acid | 12131             | 2       |
| Phoenix                 | Tartaric acid | 12Ho2-N07         | 1       |
| Caelo                   | Tartaric acid | 10b25-n05         | 1       |
| Otto Fischer            | Tartaric acid | 7020601           | 1       |
| Noweda/ Fischar         | Tartaric acid | 702061            | 1       |
| Gehe                    | Tartaric acid | 703061            | 1       |
| Fischar                 | Tartaric acid | 704061            | 2       |
| Spangropharm            | Tartaric acid | 10073111          | 1       |
| schubert / Phoenix      | Tartaric acid | 1014PLV-755       | 1       |
| Otto Fischer            | Tartaric acid | 705061            | 2       |
| Phönix Gotha            | Tartaric acid | 704021            | 1       |
| Caelo                   | Tartaric acid | 10180708          | 2       |
| ANZAG am 16.05.2012     | Tartaric acid | 10180708          | 1       |
| Caelo                   | Tartaric acid | 10180713          | 2       |
| Caelo                   | Tartaric acid | 10199713          | 1       |
| Caelo                   | Tartaric acid | 10199706          | 1       |
| Caelo                   | Tartaric acid | 10180714          | 1       |
| Phönix                  | Tartaric acid | 1106023-01        | 1       |
| Caelo                   | Tartaric acid | 11169406          | 2       |
| Fagron                  | Tartaric acid | 1106211053        | 1       |
| Caelo                   | Tartaric acid | 1169406           | 1       |
| Phönix                  | Tartaric acid | 11e24-n06         | 1       |
| Fagron                  | Tartaric acid | 11E24-N06         | 1       |
| Fagron                  | Tartaric acid | 11E24-N060752/764 | 2       |
| ANZAG am 15.05.2012     | Tartaric acid | 1108049-01        | 1       |
| Noweda                  | Tartaric acid | 11G19-N08         | 1       |
| Caelo                   | Tartaric acid | 1204102           | 1       |
| Caelo                   | Tartaric acid | 12044101          | 2       |
| Euro OTC                | Tartaric acid | 12044101          | 1       |
| Caelo                   | Tartaric acid | 12044102          | 4       |
| Caelo                   | Tartaric acid | 12044103          | 4       |
| Caesar & Loretz/ Noweda | Tartaric acid | 12044103          | 1       |
| Caelo                   | Tartaric acid | 12044112          | 1       |
| Caelo                   | Tartaric acid | 12044119          | 3       |
| Phoenix                 | Tartaric acid | 12044115          | 1       |
| Caelo                   | Tartaric acid | 12240413          | 1       |
| Caelo                   | Tartaric acid | 12286903          | 2       |
| Caelo                   | Tartaric acid | 12240402          | 1       |
| Caelo                   | Tartaric acid | 12240415          | 1       |
| Phönix                  | Tartaric acid | 12286904          | 1       |
| Caelo                   | Tartaric acid | 12286904          | 1       |
| canea, anzag            | Tartaric acid | 12286906          | 1       |
| Caelo                   | Tartaric acid | 12286906          | 3       |
| Caelo                   | Tartaric acid | 12286911          | 1       |
| Caelo                   | Tartaric acid | 12286924          | 1       |
| Caelo                   | Tartaric acid | 12286934          | 1       |
| Caelo                   | Tartaric acid | 12286929          | 1       |
| Caelo                   | Tartaric acid | 12286939          | 1       |
| Caelo                   | Tartaric acid | 12286932          | 2       |

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| <b>Supplier</b>       | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|-----------------------|------------------|------------------|----------------|
| Caelo                 | Tartaric acid    | 12286936         | 1              |
| Fagron                | Tartaric acid    | 12F18-N02        | 1              |
| Fagron                | Tartaric acid    | 12H02-N07        | 7              |
| Caelo                 | Tartaric acid    | 12286927         | 1              |
| GEHE 14.04.2014       | Tartaric acid    | 12H02-N07        | 1              |
| Caelo                 | Tartaric acid    | 12H02-n07        | 1              |
| Fagron                | Tartaric acid    | 12K16-N02        | 2              |
| Fagron                | Tartaric acid    | 13/25-B01-285488 | 2              |
| Phoenix               | Tartaric acid    | 12K29B01         | 1              |
| Fagron                | Tartaric acid    | 13/25-B01-285487 | 1              |
| Caelo                 | Tartaric acid    | 13116306         | 3              |
| Fagron                | Tartaric acid    | 12K29-B01-285247 | 1              |
| Caelo                 | Tartaric acid    | 13116307         | 1              |
| Anzag                 | Tartaric acid    | 13116308         | 1              |
| Caelo                 | Tartaric acid    | 13116308         | 4              |
| Phoenix               | Tartaric acid    | 13116308         | 1              |
| Caelo                 | Tartaric acid    | 13217806         | 2              |
| Gehe                  | Tartaric acid    | 1325-B01-285487  | 1              |
| Fagron                | Tartaric acid    | 1325-B01-294093  | 1              |
| Fagron                | Tartaric acid    | 1325-B01-285488  | 1              |
| Fagron                | Tartaric acid    | 13B15N01         | 1              |
| Caelo                 | Tartaric acid    | 13B15-N01        | 3              |
| Fragon/Sanacorp       | Tartaric acid    | 13G03-N14        | 3              |
| GEHE 14.04.2014       | Tartaric acid    | 13G03-N14        | 2              |
| Fagron                | Tartaric acid    | 13I25-B01-285488 | 2              |
| Fagron                | Tartaric acid    | 13I25-B01-294094 | 3              |
| Fagron                | Tartaric acid    | 13I25-B01-294093 | 1              |
| Fagron                | Tartaric acid    | 13I25-B01-294095 | 1              |
| Caelo                 | Tartaric acid    | 13I25-B01-294093 | 1              |
| Fagron                | Tartaric acid    | 13I25-B01-285488 | 1              |
| Caelo                 | Tartaric acid    | 14054521         | 1              |
| Fagron                | Tartaric acid    | 14G07-B02        | 1              |
| Fagron                | Tartaric acid    | 14186212         | 1              |
| Fagron                | Tartaric acid    | 14G07-B02-308554 | 1              |
| Caelo                 | Tartaric acid    | 15045302         | 2              |
| Caelo                 | Tartaric acid    | 14G07-B02-308555 | 1              |
| Caelo                 | Tartaric acid    | 14186213         | 3              |
| Caelo                 | Tartaric acid    | 15045304         | 1              |
| Caelo                 | Tartaric acid    | 15130201         | 4              |
| Caelo                 | Tartaric acid    | 15045303         | 1              |
| Caelo                 | Tartaric acid    | 15130205         | 2              |
| Caelo                 | Tartaric acid    | 151302           | 1              |
| Caelo                 | Tartaric acid    | 15164001         | 4              |
| Caelo                 | Tartaric acid    | 15130206         | 1              |
| Caelo                 | Tartaric acid    | 15164002         | 2              |
| Caelo                 | Tartaric acid    | 15164008         | 2              |
| Caelo                 | Tartaric acid    | 15349101         | 1              |
| Caelo                 | Tartaric acid    | 15349102         | 2              |
| Caelo                 | Tartaric acid    | 15349105         | 1              |
| Caelo                 | Tartaric acid    | 15349106         | 2              |
| Caelo                 | Tartaric acid    | 15349109         | 1              |
| Fagron                | Tartaric acid    | 2405211053       | 1              |
| Caelo                 | Tartaric acid    | 17091402         | 1              |
| Fagron                | Tartaric acid    | 2414E1053        | 1              |
| Fagron                | Tartaric acid    | 2112I-01053      | 1              |
| Fagron                | Tartaric acid    | 20151112-2       | 1              |
| Gehe                  | Tartaric acid    | 7284696          | 1              |
| Phönix 28.08.2012     | Tartaric acid    | 702061           | 1              |
| Fagron                | Tartaric acid    | 2513M01053       | 1              |
| Gatt-Koller / Phoenix | Tartaric acid    | 3334/08131514    | 1              |

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| Supplier | Substance     | Batch       | Spectra |
|----------|---------------|-------------|---------|
| Caelo    | Tartaric acid | 11k10-n07   | 1       |
| Caelo    | Tartaric acid | 9494239     | 1       |
| Fagron   | Tartaric acid | 10024       | 1       |
| Caelo    | Tartaric acid | 4110N-01053 | 1       |
| Caelo    | Tartaric acid |             | 1       |
| Fagron   | Tartaric acid | xxxxxxx     | 1       |

- 69 452 spectra from 414 *Apo-Ident* customers from a total of 23 697 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tartaric acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tartaric acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 270           | 0              | 146 459       |
| <b>Type C</b> | 0              | 174           | 7              | 69 452        |

The substance/substance group *Tartaric acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.7778 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 96.1326 % (> 94.4751 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22383     | 22613               | 4.94                         | 30.29                           |
| 22384     | 22384               | 0.00                         | 27.03                           |
| 22391     | 22391               | 0.00                         | 25.91                           |
| 22501     | 22391               | 2.37                         | 27.89                           |
| 22613     | 22613               | 0.00                         | 30.98                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Taurine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20403-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Taurine; Taurinum

### Special notes

When selecting the *Taurine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Taurine*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Euro OTC | Taurine   | 1306024-01 | 21108     | 40      | 20130822    |
| Euro OTC | Taurine   | 1504032-01 | 21893     | 40      | 20150430    |
| Euro OTC | Taurine   | 1504032-01 | 21992     | 40      | 9167        |
| Euro OTC | Taurine   | 1602011    | 22370     | 40      | 20160218*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Taurine*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 190 spectra of 7 reference samples from the substance/substance group *Taurine*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Fagron   | Taurine   | 10K15-N01  | 20403              | 40      |
| Euro OTC | Taurine   | 1306024-01 | 21108 <sup>†</sup> | 10      |
| Euro OTC | Taurine   | 1504032-01 | 21893 <sup>†</sup> | 20      |
| Euro OTC | Taurine   | 1504032-01 | 21992 <sup>†</sup> | 20      |
| Euro OTC | Taurine   | 1602011    | 22370 <sup>†</sup> | 20      |
| Euro OTC | Taurine   | 1607035    | 22795              | 40      |
| Euro OTC | Taurine   | 1704001    | 23177              | 40      |

- 146 539 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 23 spectra from 5 *Apo-Ident* customers from 9 batches from the substance/substance group *Taurine*.

| Supplier              | Substance | Batch      | Spectra |
|-----------------------|-----------|------------|---------|
| Pharmorgana           | Taurine   | 1000140138 | 1       |
| Gehe 18.06.2013       | Taurine   | 1106088    | 1       |
| Euro OTC              | Taurine   | 1111012-01 | 1       |
| Euro OTC              | Taurine   | 1203018-01 | 3       |
| El Compra Import      | Taurine   | 1202125    | 1       |
| hannes                | Taurine   | 1202125    | 1       |
| Euro OTC              | Taurine   | 1302016-01 | 5       |
| Euro OTC              | Taurine   | 1306024-01 | 7       |
| Euro OTC              | Taurine   | 1306024-02 | 2       |
| Gall Pharma / Phoenix | Taurine   |            | 1       |

- 69 610 spectra from 414 *Apo-Ident* customers from a total of 23 792 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Taurine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Taurine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 190           | 0              | 146 539       |
| <b>Type C</b> | 0              | 23            | 0              | 69 610        |

The substance/substance group *Taurine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.8421 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 73.9130 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21108     | 22370               | 2.35                         | 46.02                           |
| 21893     | 21992               | 1.00                         | 48.07                           |
| 21992     | 21992               | 0.00                         | 47.11                           |
| 22370     | 22370               | 0.00                         | 46.88                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Testosterone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20961-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Testosterone; Testosteronum

### Special notes

When selecting the *Testosterone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Testosterone*:

| Supplier | Substance    | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------|------------------|-----------|---------|-------------|
| Fagron   | Testosterone | 12F13-N02        | 20729     | 40      | 20120628    |
| Euro OTC | Testosterone | 1307001-01       | 20961     | 40      | 1402309     |
| Caelo    | Testosterone | 13406004         | 21370     | 40      | 20131219    |
| Fagron   | Testosterone | 15E18-B08-307772 | 21970     | 40      | 20150526    |
| Caelo    | Testosterone | 15244906         | 21987     | 40      | 20150814    |

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| Supplier | Substance    | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------|------------------|-----------|---------|-------------|
| Euro OTC | Testosterone | 1511005          | 22232     | 40      | 20151119*   |
| Euro OTC | Testosterone | 1604049          | 22561     | 40      | 20160510*   |
| Caelo    | Testosterone | 16311506         | 23244     | 40      | 20161123    |
| Fagron   | Testosterone | 15E18-B08-307772 | 21970SI   | 35      | 20150526    |
| Caelo    | Testosterone | 15244906         | 21987SI   | 24      | 20150814    |
| Euro OTC | Testosterone | 1511005          | 22232SI   | 25      | 20151119*   |
| Euro OTC | Testosterone | 1604049          | 22561SI   | 34      | 20160510*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 438 spectra of 12 reference samples from the substance/substance group *Testosterone*. These samples are listed above in the [calibration samples](#) section.
- 70948 spectra from a total of 1544 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 614 spectra of 20 reference samples from the substance/substance group *Testosterone*.

| Supplier | Substance    | Batch            | Sample ID            | Spectra |
|----------|--------------|------------------|----------------------|---------|
| Fagron   | Testosterone | 10F14-N01        | 20242                | 40      |
| Euro OTC | Testosterone | 1106011-01       | 20591                | 40      |
| Caelo    | Testosterone | 13406004         | 21371                | 40      |
| Fagron   | Testosterone | 15E18-B08-307772 | 21970 <sup>†</sup>   | 20      |
| Caelo    | Testosterone | 15244906         | 21987 <sup>†</sup>   | 20      |
| Euro OTC | Testosterone | 1511005-01       | 21994                | 60      |
| Euro OTC | Testosterone | 1511005          | 22232 <sup>†</sup>   | 20      |
| Euro OTC | Testosterone | 1607013          | 22707                | 40      |
| Euro OTC | Testosterone | 1702017          | 23146                | 40      |
| Caelo    | Testosterone | 171199           | 23347                | 40      |
| Caelo    | Testosterone | 171199           | 23670                | 30      |
| Fagron   | Testosterone | 15E18-B08-307772 | 21970SI <sup>†</sup> | 19      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.



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| Supplier | Substance    | Batch      | Sample ID            | Spectra |
|----------|--------------|------------|----------------------|---------|
| Caelo    | Testosterone | 15244906   | 21987SI <sup>†</sup> | 14      |
| Euro OTC | Testosterone | 1511005-01 | 21994SI              | 32      |
| Euro OTC | Testosterone | 1511005    | 22232SI <sup>†</sup> | 10      |
| Euro OTC | Testosterone | 1607013    | 22707SI              | 40      |
| Euro OTC | Testosterone | 1702017    | 23146SI              | 21      |
| Caelo    | Testosterone | 16311506   | 23244SI              | 30      |
| Caelo    | Testosterone | 171199     | 23347SI              | 28      |
| Caelo    | Testosterone | 171199     | 23670SI              | 30      |

- 146 115 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 68 spectra from 34 *Apo-Ident* customers from 40 batches from the substance/substance group *Testosterone*.

| Supplier      | Substance    | Batch            | Spectra |
|---------------|--------------|------------------|---------|
| Caelo         | Testosterone | 11/07-N12        | 2       |
| EuRho         | Testosterone | 1106011-03       | 2       |
| Caelo         | Testosterone | 12176305         | 3       |
| Caelo         | Testosterone |                  | 1       |
| Euro OTC      | Testosterone | 1307001-01       | 6       |
| Caelo         | Testosterone | 13134806         | 4       |
| Euroo/Phoenix | Testosterone | 1307001-01       | 1       |
| Spirig        | Testosterone | 13406003         | 1       |
| Caelo         | Testosterone | 13406004         | 2       |
| Fagron        | Testosterone | 13G10-N03        | 2       |
| Fagron        | Testosterone | 13I26-N08        | 1       |
| Fagron        | Testosterone | 13L09-B03-294148 | 1       |
| Fagron        | Testosterone | 13L09-B03-294149 | 1       |
| Euro OTC      | Testosterone | 1404002-01       | 2       |
| Euro OTC      | Testosterone | 1404002-1        | 1       |
| Euro OTC      | Testosterone | 140400201        | 1       |
| Caelo         | Testosterone | 14355605         | 1       |
| Caelo         | Testosterone | 14201105         | 1       |
| Phönix Gotha  | Testosterone | 1408015-01       | 1       |
| Euro OTC      | Testosterone | 1408015-01       | 1       |
| Euro OTC      | Testosterone | 1511005-01       | 1       |
| Caelo         | Testosterone | 15195802         | 1       |
| Caelo         | Testosterone | 15195803         | 1       |
| Caelo         | Testosterone | 15412201         | 1       |
| Caelo         | Testosterone | 15412202         | 1       |
| Euro OTC      | Testosterone | 1604049-01       | 1       |
| Caelo         | Testosterone | 1604049-01       | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier                   | Substance    | Batch        | Spectra |
|----------------------------|--------------|--------------|---------|
| Caelo                      | Testosterone | 16225807     | 2       |
| NWM CHina                  | Testosterone | TE150402     | 1       |
| Shandong Northwest Manu... | Testosterone | GTJ160510    | 1       |
| Euro OTC                   | Testosterone | 1106011-01   | 2       |
| Fagron                     | Testosterone | GTJ151103    | 1       |
| Euro OTC                   | Testosterone | 1106011-03   | 2       |
| Phönix Gotha               | Testosterone | 1106011-03   | 1       |
| Euro OTC                   | Testosterone | 110611-003   | 1       |
| Euro OTC                   | Testosterone | 1106011-03   | 1       |
| Klenk                      | Testosterone | 12176305     | 1       |
| Euro OTC                   | Testosterone | 1207005-02   | 2       |
| Großhandel                 | Testosterone | 12F13-N02    | 1       |
| Caelo                      | Testosterone | 13134804     | 1       |
| Großhandel                 | Testosterone | 13610-N03    | 1       |
| Haihang Industry           | Testosterone | 20140114-1   | 1       |
| Großhandel                 | Testosterone | 13G10-N03    | 1       |
| Caelo                      | Testosterone | APL00034466T | 1       |
| Fagron                     | Testosterone | 12F13-N02    | 1       |
| Euro OTC                   | Testosterone | 3x1106011-03 | 1       |
| Haihang Industry           | Testosterone | 20140114-2   | 1       |
| EUro/AHD                   | Testosterone | 1106011-03   | 1       |
| Caelo                      | Testosterone | 12176301     | 1       |

- 69 565 spectra from 414 *Apo-Ident* customers from a total of 23 762 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Testosterone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Testosterone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 438           | 0              | 70 948        |
| <b>Type B</b> | 0              | 602           | 12             | 146 115       |
| <b>Type C</b> | 0              | 64            | 4              | 69 565        |

The substance/substance group *Testosterone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.6301 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 98.0456 % (> 97.5570 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 94.1176 % (> 89.7059 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20729     | 22232               | 16.41                        | 40.25                           |
| 20961     | 20961               | 0.00                         | 24.79                           |
| 21370     | 20961               | 8.23                         | 29.42                           |
| 21970     | 22232               | 3.26                         | 26.98                           |
| 21987     | 22232               | 3.21                         | 29.96                           |
| 22232     | 22232               | 0.00                         | 32.78                           |
| 22561     | 22561               | 0.00                         | 36.39                           |
| 23244     | 20961               | 5.77                         | 24.94                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Testosterone propionate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20880-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Testosterone propionate; Testosteroni propionas; Testosteronum propionicum

### Special notes

When selecting the *Testosterone propionate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Testosterone propionate*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------|-----------|---------|--------------------|
| Caelo    | Testosterone pro... | 12163607   | 20880     | 40      | AR-15-FG-000623-01 |
| Euro OTC | Testosterone pro... | 1109024-02 | 21644     | 40      | 1503607            |
| Euro OTC | Testosterone pro... | 1511003    | 22230     | 40      | 20151111*          |
| Euro OTC | Testosterone pro... | 1512023    | 22288     | 30      | 20151230*          |
| Caelo    | Testosterone pro... | 15444709   | 23170     | 40      | 1707612            |
| Euro OTC | Testosterone pro... | 1511003    | 22230SI   | 28      | 20151111*          |
| Euro OTC | Testosterone pro... | 1512023    | 22288SI   | 30      | 20151230*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 248 spectra of 7 reference samples from the substance/substance group *Testosterone propionate*. These samples are listed above in the [calibration samples](#) section.
- 71 138 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 184 spectra of 8 reference samples from the substance/substance group *Testosterone propionate*.

| Supplier | Substance               | Batch      | Sample ID            | Spectra |
|----------|-------------------------|------------|----------------------|---------|
| Euro OTC | Testosterone propionate | 1109024-02 | 21644 <sup>†</sup>   | 20      |
| Euro OTC | Testosterone propionate | 1511003    | 22230 <sup>†</sup>   | 20      |
| Euro OTC | Testosterone propionate | 1512023    | 22288 <sup>†</sup>   | 15      |
| Caelo    | Testosterone propionate | 170963     | 23334                | 40      |
| Euro OTC | Testosterone propionate | 1511003    | 22230SI <sup>†</sup> | 15      |
| Euro OTC | Testosterone propionate | 1512023    | 22288SI <sup>†</sup> | 15      |
| Caelo    | Testosterone propionate | 15444709   | 23170SI              | 30      |
| Caelo    | Testosterone propionate | 170963     | 23334SI              | 29      |

- 146 545 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 264 spectra from 132 *Apo-Ident* customers from 103 batches from the substance/substance group *Testosterone propionate*.

| Supplier       | Substance               | Batch            | Spectra |
|----------------|-------------------------|------------------|---------|
| Apomix / AHD   | Testosterone propionate | 40/14            | 1       |
| Caelo          | Testosterone propionate | 10L03-N16        | 2       |
| Fagron         | Testosterone propionate | 11G15-N07        | 2       |
| Euro OTC       | Testosterone propionate | 1109024-03       | 1       |
| Euro OTC       | Testosterone propionate | 1109024-01       | 1       |
| Caelo          | Testosterone propionate | 1109024-02       | 1       |
| Caelo          | Testosterone propionate | 12163610         | 3       |
| Caelo          | Testosterone propionate | 12163612         | 6       |
| phoenix        | Testosterone propionate | 12163615         | 1       |
| Phönix         | Testosterone propionate | 12163613         | 1       |
| Caelo          | Testosterone propionate | 12163616         | 4       |
| Caelo          | Testosterone propionate | 12163617         | 4       |
| Caelo          | Testosterone propionate | 12163619         | 2       |
| Phönix         | Testosterone propionate | 12163617         | 1       |
| Caelo          | Testosterone propionate | 12163621         | 1       |
| Fagron         | Testosterone propionate | 13C08-N02        | 14      |
| Fagron         | Testosterone propionate | 13F05-N04        | 18      |
| Caelo          | Testosterone propionate | 13C08-N02        | 1       |
| Fagron         | Testosterone propionate | 13I03-N02        | 1       |
| Phönix         | Testosterone propionate | 13K25-B05        | 1       |
| Fagron         | Testosterone propionate | 13K25-B05        | 1       |
| Fagron         | Testosterone propionate | 13K25-B05-287647 | 11      |
| Fagron         | Testosterone propionate | 13K25-B05-287648 | 4       |
| apomix         | Testosterone propionate | 13K25-B05-287648 | 1       |
| Fagron         | Testosterone propionate | 13K25B05287648   | 1       |
| Fagron         | Testosterone propionate | 13K25-B05-291974 | 2       |
| Euro OTC       | Testosterone propionate | 1409037-01       | 1       |
| Fagron         | Testosterone propionate | 14A28-B12        | 2       |
| Fagron         | Testosterone propionate | 14A28-B12-291977 | 1       |
| Fagron         | Testosterone propionate | 14A28-B12-296958 | 1       |
| Fagron         | Testosterone propionate | 14A28-B12-296960 | 2       |
| Fagron         | Testosterone propionate | 14D15-B03-296959 | 4       |
| Fagron         | Testosterone propionate | 14L31-B02        | 2       |
| Fagron         | Testosterone propionate | 14L31-B02-304721 | 6       |
| Fagron         | Testosterone propionate | 14L31B02-304721  | 1       |
| Fagron         | Testosterone propionate | 14L31-B02-304722 | 8       |
| Caelo          | Testosterone propionate | 14L31-B02-304722 | 2       |
| Fagron         | Testosterone propionate | 14L31B02304722   | 1       |
| Caelo          | Testosterone propionate | 15003002         | 9       |
| Fagron         | Testosterone propionate | 15/01-B09-318371 | 1       |
| Caelo          | Testosterone propionate | 15003008         | 1       |
| Fagron         | Testosterone propionate | 1501-B09-312867  | 1       |
| Euro OTC       | Testosterone propionate | 1504023-01       | 1       |
| Euro OTC       | Testosterone propionate | 1511003-01       | 6       |
| Caelo          | Testosterone propionate | 15169504         | 1       |
| Caelo          | Testosterone propionate | 15444703         | 7       |
| Phönix         | Testosterone propionate | 15444702         | 1       |
| Caelo          | Testosterone propionate | 15444702         | 1       |
| Ebert 17.08.16 | Testosterone propionate | 15444703         | 1       |
| Gehe           | Testosterone propionate | 15444706         | 1       |
| Caelo          | Testosterone propionate | 15444706         | 1       |
| Caelo          | Testosterone propionate | 15444707         | 1       |
| Fagron         | Testosterone propionate | 15D03-B02-310694 | 1       |
| Fagron         | Testosterone propionate | 15I01-B09-312867 | 2       |

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| <b>Supplier</b> | <b>Substance</b>        | <b>Batch</b>         | <b>Spectra</b> |
|-----------------|-------------------------|----------------------|----------------|
| Fagron          | Testosterone propionate | 15k03-b03            | 1              |
| Fagron          | Testosterone propionate | 15K03-B03-315218     | 5              |
| Fagron          | Testosterone propionate | 15K03-B-03-315218    | 1              |
| Galderma        | Testosterone propionate | 15K03-B03-315218     | 1              |
| Fagron          | Testosterone propionate | 16C24-B04-320784     | 2              |
| Fagron          | Testosterone propionate | 16E24-B01-322593     | 3              |
| Fagron          | Testosterone propionate | 16H22-B05-326482     | 1              |
| Fagron          | Testosterone propionate | 16H22-B05            | 1              |
| Fagron          | Testosterone propionate | 16H22-B05-326483     | 1              |
| Fagron          | Testosterone propionate | 36513M1              | 2              |
| Fagron          | Testosterone propionate | 36814M1              | 1              |
| Caelo           | Testosterone propionate | 36814M1              | 1              |
| Caelo           | Testosterone propionate | 36814m1              | 1              |
| Audor Pharma    | Testosterone propionate | AP1109024-03         | 2              |
| Audor Pharma    | Testosterone propionate | AP1109024-03TP       | 4              |
| Audor Pharma    | Testosterone propionate | APZTSP15003-MTP      | 3              |
| Audor Pharma    | Testosterone propionate | AP12J10-N08TP        | 2              |
| Audor Pharma    | Testosterone propionate | AP13K25-B05-287643TP | 1              |
| Caelo           | Testosterone propionate | 12J10-N08            | 2              |
| Caelo           | Testosterone propionate | 106212376            | 1              |
| Caelo           | Testosterone propionate | 614E2376             | 1              |
| Caelo           | Testosterone propionate | 903312376            | 1              |
| Fagron          | Testosterone propionate | 6081201              | 1              |
| Caelo           | Testosterone propionate | 612212376            | 1              |
| Caelo           | Testosterone propionate | 10235809             | 1              |
| Caelo           | Testosterone propionate | 10235821             | 1              |
| Finze           | Testosterone propionate | 10366002             | 1              |
| Fargron         | Testosterone propionate | 10L03-N16            | 1              |
| Fagron          | Testosterone propionate | 11/12-N03            | 1              |
| Euro OTC        | Testosterone propionate | 1103010-01           | 2              |
| Fagron          | Testosterone propionate | 10L03-N16            | 1              |
| Phönix/Euro     | Testosterone propionate | 110301002            | 1              |
| Phönix          | Testosterone propionate | 1103010-02           | 1              |
| Caelo           | Testosterone propionate | 1108212376           | 1              |
| Phoenix         | Testosterone propionate | 1109024-02           | 1              |
| Fagron          | Testosterone propionate | 11K18-N04            | 5              |
| Fagron          | Testosterone propionate | 11C21-N09            | 1              |
| Andor           | Testosterone propionate | 1109024-03TP         | 1              |
| Noweda          | Testosterone propionate | 11K18-N04            | 1              |
| Caelo           | Testosterone propionate | 11K18-N04            | 1              |
| Fargron         | Testosterone propionate | 11K18-N04            | 1              |
| Fagron          | Testosterone propionate | 12/10-N08            | 1              |
| Fagron          | Testosterone propionate | 12C01-N01            | 1              |
| Caelo           | Testosterone propionate | 12060102             | 3              |
| Caelo           | Testosterone propionate | 12163605             | 1              |
| Caelo           | Testosterone propionate | 12163607             | 1              |
| Caelo           | Testosterone propionate | 12163615             | 1              |
| Fagron          | Testosterone propionate | 12163616             | 2              |
| Caelo           | Testosterone propionate | 1263607              | 1              |
| Fagron          | Testosterone propionate | 12A02-N05            | 5              |
| Caelo           | Testosterone propionate | 12A02-N05            | 1              |
| Fagron          | Testosterone propionate | 12E04-N01            | 4              |
| Fagron          | Testosterone propionate | 12C01-N01            | 1              |
| Fagron          | Testosterone propionate | 12J10-N08            | 3              |
| Fagron          | Testosterone propionate | 12E29-N02            | 1              |
| Fagron          | Testosterone propionate | 12J10N-08            | 1              |
| Phönix          | Testosterone propionate | 12J10-N08            | 1              |
| Fagron          | Testosterone propionate | 13/03-N02            | 1              |
| Phönix          | Testosterone propionate | 13C08-N02            | 2              |
| Fagron          | Testosterone propionate | 13C08N02             | 1              |

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| Supplier         | Substance               | Batch               | Spectra |
|------------------|-------------------------|---------------------|---------|
| Jenne            | Testosterone propionate | 13C08-N02           | 1       |
| Caelo            | Testosterone propionate | 2013U-02376         | 1       |
| Fagron           | Testosterone propionate | 20121012-3          | 1       |
| Fagron           | Testosterone propionate | 24411M1             | 1       |
| Fagron           | Testosterone propionate | 32012M1             | 3       |
| Euro OTC         | Testosterone propionate | 970116/1            | 1       |
| Fagron           | Testosterone propionate | 3613M-02376         | 1       |
| Audor Pharma     | Testosterone propionate | AP12E04N01TP        | 2       |
| Anzag 21.02.2013 | Testosterone propionate | AP12E04-N01TP       | 1       |
| Anzag 04.09.12   | Testosterone propionate | AP12E04-N01TP       | 1       |
| AHD              | Testosterone propionate | AP12E04-N01TP       | 1       |
| Audor Pharma     | Testosterone propionate | AP-12J10-N08Tp      | 1       |
| Audor Pharma     | Testosterone propionate | AP13K25-B05-287643T | 1       |
| Fagron           | Testosterone propionate |                     | 1       |

- 69 369 spectra from 414 *Apo-Ident* customers from a total of 23 699 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Testosterone propionate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Testosterone propionate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 248           | 0              | 71 138        |
| <b>Type B</b> | 0              | 184           | 0              | 146 545       |
| <b>Type C</b> | 0              | 261           | 3              | 69 369        |

The substance/substance group *Testosterone propionate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.5806 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.7391 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 98.8636 % (> 97.7273 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20880     | 20880               | 0.00                         | 7.98                            |
| 21644     | 21644               | 0.00                         | 6.65                            |
| 22230     | 22230               | 0.00                         | 8.41                            |
| 22288     | 22288               | 0.00                         | 8.54                            |
| 23170     | 23170               | 0.00                         | 7.63                            |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tetracaine base**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20947-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tetracaine base; Tetracainum

### Special notes

When selecting the *Tetracaine base* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tetracaine base*:

| Supplier | Substance       | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------------|------------------|-----------|---------|--------------------|
| Fagron   | Tetracaine base | 12L19-N10        | 20947     | 40      | 20130108           |
| Euro OTC | Tetracaine base | 1405025-01       | 21603     | 40      | AR-14-FG-012475-01 |
| Fagron   | Tetracaine base | 14A16-B04-292915 | 21650     | 40      | 20140205           |
| Fagron   | Tetracaine base | 14A16-B04-292916 | 21659     | 40      | 20140205           |
| Euro OTC | Tetracaine base | 1512022          | 22299     | 30      | 20160128*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 190 spectra of 5 reference samples from the substance/substance group *Tetracaine base*. These samples are listed above in the [calibration samples](#) section.
- 71 196 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 335 spectra of 9 reference samples from the substance/substance group *Tetracaine base*.

| Supplier | Substance       | Batch            | Sample ID          | Spectra |
|----------|-----------------|------------------|--------------------|---------|
| Fagron   | Tetracaine base | 10H05-N08        | 20231              | 40      |
| Euro OTC | Tetracaine base | 1405025-01       | 21603 <sup>†</sup> | 20      |
| Fagron   | Tetracaine base | 14A16-B04-292915 | 21650 <sup>†</sup> | 80      |
| Fagron   | Tetracaine base | 14A16-B04-292916 | 21659 <sup>†</sup> | 20      |
| Euro OTC | Tetracaine base | 1512022          | 22299 <sup>†</sup> | 15      |
| Euro OTC | Tetracaine base | 1606009          | 22717              | 40      |
| Euro OTC | Tetracaine base | 1609010          | 22858              | 40      |
| Euro OTC | Tetracaine base | 1701035          | 23149              | 40      |
| Caelo    | Tetracaine base | 171117           | 23321              | 40      |

- 146 394 spectra from a total of 3185 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 121 spectra from 46 *Apo-Ident* customers from 56 batches from the substance/substance group *Tetracaine base*.

| Supplier          | Substance       | Batch             | Spectra |
|-------------------|-----------------|-------------------|---------|
| Euro OTC          | Tetracaine base | 10887133          | 1       |
| Euro OTC          | Tetracaine base | 12081501          | 1       |
| Euro OTC          | Tetracaine base | 1312034-01        | 8       |
| Phönix            | Tetracaine base | 1312034-01        | 1       |
| GEHE 04.05        | Tetracaine base | 1405025-01        | 1       |
| Fagron            | Tetracaine base | 14A16-B04         | 1       |
| Fagron            | Tetracaine base | 14A16-B04-290208  | 3       |
| Caelo             | Tetracaine base | 14A16-B04-290207  | 1       |
| GEHE 02.05.2014   | Tetracaine base | 14A16-B04-290208  | 3       |
| Fagron            | Tetracaine base | 14A16-B04-2490207 | 1       |
| Fagron            | Tetracaine base | 14a16-b04-290208  | 1       |
| Phoenix 07.10.14  | Tetracaine base | 14A16-B04-292916  | 1       |
| Fagron            | Tetracaine base | 14A16-B04-292916  | 1       |
| Fagron            | Tetracaine base | 14G30-B08         | 2       |
| Caelo             | Tetracaine base | 14A16-B04-292916  | 1       |
| Fagron            | Tetracaine base | 14g30-b08-297306  | 1       |
| Fagron            | Tetracaine base | 14G30-B08-297306  | 3       |
| Phoenix Goettin   | Tetracaine base | 14G30-B08-297306  | 1       |
| Fagron            | Tetracaine base | 15/16-B06-312783  | 2       |
| Fagron            | Tetracaine base | 14K03-B02-303179  | 2       |
| Fagron            | Tetracaine base |                   | 1       |
| Fagron            | Tetracaine base | 14K03-B02         | 1       |
| Euro OTC          | Tetracaine base | 151022-01         | 1       |
| Caelo             | Tetracaine base | 1512022-01        | 1       |
| Faron             | Tetracaine base | 15D01-B03-306258  | 2       |
| Fagron            | Tetracaine base | 1516-B06-316259   | 1       |
| Caelo             | Tetracaine base | 16/AKD12          | 1       |
| Hepart            | Tetracaine base | 15G30-B04-310590  | 1       |
| Fagron            | Tetracaine base | 15D01-B03-306258  | 1       |
| Euro OTC          | Tetracaine base | 160600-01         | 1       |
| Fagron            | Tetracaine base | 1606009-01        | 1       |
| Euro OTC          | Tetracaine base | 1606009-01        | 3       |
| Fagron            | Tetracaine base | 15G30-B04-312060  | 1       |
| Euro OTC          | Tetracaine base | 1609010-01        | 5       |
| Fagron            | Tetracaine base | 16A13-B07-318736  | 3       |
| Caelo             | Tetracaine base | 16a13-b07-318736  | 1       |
| Fagron            | Tetracaine base | 16E23-B04-323269  | 1       |
| Ebert-Jacobi      | Tetracaine base | 16J12-B06-327371  | 1       |
| Caelo             | Tetracaine base | 16A13-B07-318736  | 2       |
| Fagron            | Tetracaine base | 16G29B02325570    | 2       |
| Fagron            | Tetracaine base | TC0090913         | 2       |
| Fagron            | Tetracaine base | 2913Q-07165       | 1       |
| Fagron            | Tetracaine base | 11D07-N20         | 1       |
| Fargron           | Tetracaine base | 11G12-N13         | 1       |
| Phönix            | Tetracaine base | 11g12-n13         | 1       |
| Phönix            | Tetracaine base | 3465093           | 1       |
| Euro OTC          | Tetracaine base | TC0091115         | 1       |
| Fagron            | Tetracaine base | 11G12-N13         | 4       |
| Fagron            | Tetracaine base | 5111202           | 1       |
| Fagron            | Tetracaine base | 11L09-N03         | 3       |
| Fagron            | Tetracaine base | 11101-N09         | 1       |
| Phönix 19.06.2012 | Tetracaine base | 11L09-N03         | 1       |

*continued on the next page*

continued from previous page

| Supplier           | Substance       | Batch            | Spectra |
|--------------------|-----------------|------------------|---------|
| Fagron             | Tetracaine base | 12115008         | 1       |
| Fagron             | Tetracaine base | 12F26-N05        | 2       |
| Fagron             | Tetracaine base | 12F29-N05        | 7       |
| Fagron             | Tetracaine base | 12f29-n05        | 1       |
| Phoenix 26.03.2013 | Tetracaine base | 12F29-N05        | 1       |
| Fagron             | Tetracaine base | 12H23-N07        | 2       |
| phönix, 14.11.2012 | Tetracaine base | 12F-29-N05       | 1       |
| Fagron             | Tetracaine base | 12L19-N10        | 6       |
| Anzag 08.03.2013   | Tetracaine base | 12L19-N10        | 2       |
| Phönix             | Tetracaine base | 1303018-01       | 1       |
| Fagron             | Tetracaine base | 13D30-N11        | 3       |
| Caelo              | Tetracaine base | T-290413-1       | 1       |
| Fagron             | Tetracaine base | 3465093          | 1       |
| Euro OTC           | Tetracaine base | 1405025-01       | 1       |
| Fagron             | Tetracaine base | 14A16-B04-290209 | 1       |
| Fagron             | Tetracaine base | 14G30-B08-297307 | 1       |
| Fagron             | Tetracaine base | 14G30-B08-297305 | 1       |
| Caelo              | Tetracaine base | 14K03-B02-303179 | 1       |
| Fagron             | Tetracaine base | 14g30-b08-297305 | 1       |
| Caelo              | Tetracaine base | 1606009-01       | 1       |

- 69 512 spectra from 414 *Apo-Ident* customers from a total of 23 746 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tetracaine base* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tetracaine base* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 190           | 0              | 71 196        |
| <b>Type B</b> | 0              | 288           | 47             | 146 394       |
| <b>Type C</b> | 0              | 117           | 4              | 69 512        |

The substance/substance group *Tetracaine base* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.8421 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 85.9701 % (> 85.0746 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 96.6942 % (> 94.2149 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to

exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20947     | 21603               | 2.55                         | 57.00                           |
| 21603     | 21603               | 0.00                         | 57.24                           |
| 21650     | 22299               | 5.02                         | 54.71                           |
| 21659     | 21603               | 4.38                         | 58.01                           |
| 22299     | 22299               | 0.00                         | 47.93                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.





# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tetracaine hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20037-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tetracaine hydrochloride; Tetracaini hydrochloridum; Tetracainum hydrochloricum

### Special notes

When selecting the *Tetracaine hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tetracaine hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Caelo    | Tetracaine hydro... | 12019822         | 20924     | 40      | 20120228    |
| Euro OTC | Tetracaine hydro... | 1506040          | 21845     | 40      | 20150713*   |
| Euro OTC | Tetracaine hydro... | 1512019          | 22285     | 30      | 20151228*   |
| Euro OTC | Tetracaine hydro... | 1612005          | 22912     | 40      | 20170112*   |
| Fagron   | Tetracaine hydro... | 15K04-B03-322151 | 23162     | 40      | 20160112    |
| Caelo    | Tetracaine hydro... | 15437108         | 23163     | 40      | 20160211    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 230 spectra of 6 reference samples from the substance/substance group *Tetracaine hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 156 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 225 spectra of 7 reference samples from the substance/substance group *Tetracaine hydrochloride*.

| Supplier | Substance                | Batch            | Sample ID          | Spectra |
|----------|--------------------------|------------------|--------------------|---------|
| Caelo    | Tetracaine hydrochloride | 83228149         | 20037              | 30      |
| Fagron   | Tetracaine hydrochloride | 11A31-N15        | 20215              | 40      |
| Euro OTC | Tetracaine hydrochloride | 1506040          | 21845 <sup>†</sup> | 20      |
| Euro OTC | Tetracaine hydrochloride | 1512019          | 22285 <sup>†</sup> | 15      |
| Euro OTC | Tetracaine hydrochloride | 1607031          | 22708              | 40      |
| Fagron   | Tetracaine hydrochloride | 16G28-B03-327368 | 23500              | 40      |
| Euro OTC | Tetracaine hydrochloride | 1706018          | 23558              | 40      |

- 146 504 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 608 spectra from 196 *Apo-Ident* customers from 146 batches from the substance/substance group *Tetracaine hydrochloride*.

| Supplier                   | Substance                | Batch            | Spectra |
|----------------------------|--------------------------|------------------|---------|
| Euro OTC                   | Tetracaine hydrochloride | 1607031-01       | 9       |
| Euro OTC                   | Tetracaine hydrochloride | 1207001-01       | 14      |
| Euro OTC                   | Tetracaine hydrochloride | 1207001-02       | 11      |
| Großhandel                 | Tetracaine hydrochloride | 12H24-N05        | 4       |
| Caelo                      | Tetracaine hydrochloride | 1313012-01       | 1       |
| Caelo                      | Tetracaine hydrochloride | 13155711         | 10      |
| Großhandel                 | Tetracaine hydrochloride | 13D11-N07        | 7       |
| Großhandel                 | Tetracaine hydrochloride | 13H21-B02-286559 | 1       |
| Sanacorp                   | Tetracaine hydrochloride | 15/AKD1          | 1       |
| Caelo                      | Tetracaine hydrochloride |                  | 1       |
| Fagron                     | Tetracaine hydrochloride | 6093547          | 2       |
| Caelo                      | Tetracaine hydrochloride | 6093549          | 1       |
| Alliance Health 22.08.2... | Tetracaine hydrochloride | 6093549          | 1       |
| Fagron                     | Tetracaine hydrochloride | 6093549          | 1       |
| Gatt-Koller / Phoenix      | Tetracaine hydrochloride | 80/02140614      | 2       |
| Fagron                     | Tetracaine hydrochloride | 10330837         | 1       |
| Fagron                     | Tetracaine hydrochloride | 10990834         | 4       |
| Caelo                      | Tetracaine hydrochloride | 12019822         | 7       |
| gehe                       | Tetracaine hydrochloride | 12C22-N04        | 1       |
| Euro OTG                   | Tetracaine hydrochloride | 1207001-01       | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 1303012-01       | 22      |
| Alliance Health 30.04.2... | Tetracaine hydrochloride | 1303012-01       | 2       |
| Euro OTC                   | Tetracaine hydrochloride | 130301201        | 3       |
| Euro OTC                   | Tetracaine hydrochloride |                  | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 1310006-01       | 20      |
| Phoenix am 30.04.2014      | Tetracaine hydrochloride | 1310006-01       | 1       |
| EuroTOC / Noweda           | Tetracaine hydrochloride | 131000601        | 2       |
| Gehe                       | Tetracaine hydrochloride | 1310006-01       | 4       |
| Noweda                     | Tetracaine hydrochloride | 1310006-01       | 1       |
| Caelo                      | Tetracaine hydrochloride | 13155703         | 1       |
| Caelo                      | Tetracaine hydrochloride | 13155705         | 3       |
| Caelo                      | Tetracaine hydrochloride | 13155706         | 11      |
| Gehe 07.07.2014            | Tetracaine hydrochloride | 13155706         | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 13155710         | 4       |
| Fagron                     | Tetracaine hydrochloride | 13155711         | 1       |
| Gehe                       | Tetracaine hydrochloride | 13155711         | 2       |
| Caelo                      | Tetracaine hydrochloride | 13155714         | 3       |
| BASF Fine Chemicals Swi... | Tetracaine hydrochloride | 13155714         | 1       |
| Caelo                      | Tetracaine hydrochloride | 13155716         | 2       |
| Caelo                      | Tetracaine hydrochloride | 13155724         | 4       |
| Caelo                      | Tetracaine hydrochloride | 13155720         | 2       |
| Caelo                      | Tetracaine hydrochloride | 13155727         | 6       |
| Calo/AHD                   | Tetracaine hydrochloride | 13155727         | 1       |
| Fagron                     | Tetracaine hydrochloride | 13D11-N07        | 10      |
| Fagron                     | Tetracaine hydrochloride | 13H21-B02        | 2       |
| Fagron                     | Tetracaine hydrochloride | 13H21-B02-286558 | 4       |
| Alliance Health 05.05.2... | Tetracaine hydrochloride | 13H21-B02-286559 | 1       |
| Fagron                     | Tetracaine hydrochloride | 13K25-B04        | 2       |
| Fagron                     | Tetracaine hydrochloride |                  | 1       |
| Fagron                     | Tetracaine hydrochloride | 13H21-B02-286559 | 1       |
| Fagron                     | Tetracaine hydrochloride | 13K25-B04-290276 | 4       |
| Caelo                      | Tetracaine hydrochloride | 13K25-B04-290276 | 2       |
| Euro OTC                   | Tetracaine hydrochloride | 1405026-01       | 17      |
| Fagron                     | Tetracaine hydrochloride | 13K25-B04-290278 | 2       |

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| Supplier             | Substance                | Batch            | Spectra |
|----------------------|--------------------------|------------------|---------|
| euroct/gehe          | Tetracaine hydrochloride | 1405026-01       | 1       |
| Caelo                | Tetracaine hydrochloride | 1405026-01       | 1       |
| Gehe                 | Tetracaine hydrochloride | 1405026-01       | 3       |
| Phönix               | Tetracaine hydrochloride | 1405026-01       | 1       |
| Euro OTC             | Tetracaine hydrochloride | 1409026          | 1       |
| Euro OTC             | Tetracaine hydrochloride | 1405026-04       | 1       |
| Euro OTC             | Tetracaine hydrochloride | 1409026-01       | 12      |
| AHD 12.12.14 EK 6,94 | Tetracaine hydrochloride | 1409026-01       | 1       |
| Sanacorp             | Tetracaine hydrochloride | 1409026-01       | 1       |
| Phoenix Goettin      | Tetracaine hydrochloride | 1409026-01       | 1       |
| Caelo                | Tetracaine hydrochloride | 1409026-02       | 3       |
| Euro OTC             | Tetracaine hydrochloride | 1409026-02       | 7       |
| BASF Pharma S.A.     | Tetracaine hydrochloride | 1409026-02       | 1       |
| Euro OTC             | Tetracaine hydrochloride | 1411019-01       | 16      |
| EuRP/Geibo           | Tetracaine hydrochloride | 1411019-01       | 4       |
| BASF Pharma          | Tetracaine hydrochloride | 1411019-01       | 1       |
| Euro OTC             | Tetracaine hydrochloride | 141101901        | 1       |
| Fagron               | Tetracaine hydrochloride | 1411019-01       | 1       |
| Fagron               | Tetracaine hydrochloride | 14C18-B03-293966 | 5       |
| Fagron               | Tetracaine hydrochloride | 1418-03-300199   | 1       |
| Alliance Health      | Tetracaine hydrochloride | 14C18-B03-293967 | 1       |
| Fagron               | Tetracaine hydrochloride | 14C18-B03-293967 | 3       |
| Fagron               | Tetracaine hydrochloride | 14C18-B03-300199 | 3       |
| Caelo                | Tetracaine hydrochloride | 14C18-B03-300200 | 1       |
| Caelo                | Tetracaine hydrochloride | 14C18-B03-300199 | 1       |
| Fagron               | Tetracaine hydrochloride | 14C18-B03-300200 | 4       |
| Fagron               | Tetracaine hydrochloride | 14C18-Bo3-300200 | 1       |
| Fagron               | Tetracaine hydrochloride | 14c18d03300199   | 1       |
| Caelo                | Tetracaine hydrochloride | 14G14-B08        | 1       |
| Fagron               | Tetracaine hydrochloride | 14G14-B08-300198 | 2       |
| Caelo                | Tetracaine hydrochloride | 14G14-B08-300198 | 1       |
| Euro/Phönix          | Tetracaine hydrochloride | 1506040-01       | 1       |
| Euro OTC             | Tetracaine hydrochloride | 1506040-01       | 17      |
| Caelo                | Tetracaine hydrochloride | 150604001        | 1       |
| Euro OTC             | Tetracaine hydrochloride | 1506040-02       | 6       |
| Caelo                | Tetracaine hydrochloride | 15079501         | 2       |
| Caelo                | Tetracaine hydrochloride | 15079507         | 2       |
| Euro OTC             | Tetracaine hydrochloride | 15120019-01      | 1       |
| Euro OTC             | Tetracaine hydrochloride | 1512019-01       | 12      |
| Caelo                | Tetracaine hydrochloride | 1512019-01       | 2       |
| Euro OTC             | Tetracaine hydrochloride | 151-2019-01      | 1       |
| Caelo                | Tetracaine hydrochloride | 1512019-02       | 1       |
| Caelo                | Tetracaine hydrochloride | 15196102         | 4       |
| Caelo                | Tetracaine hydrochloride | 15196103         | 4       |
| Caelo                | Tetracaine hydrochloride | 15196104         | 2       |
| Caelo                | Tetracaine hydrochloride | 15437102         | 1       |
| Phoenix              | Tetracaine hydrochloride | 15437104         | 2       |
| Caelo                | Tetracaine hydrochloride | 15437104         | 13      |
| Caelo                | Tetracaine hydrochloride | 15356902         | 2       |
| Caelo                | Tetracaine hydrochloride | 15437106         | 3       |
| Caelo                | Tetracaine hydrochloride | 15437109         | 7       |
| Fagron               | Tetracaine hydrochloride | 15437117         | 1       |
| Fagron               | Tetracaine hydrochloride | 15A12-B03-308857 | 4       |
| Fagron               | Tetracaine hydrochloride | 15A12-B03        | 1       |
| Caelo                | Tetracaine hydrochloride | 15437119         | 1       |
| Caelo                | Tetracaine hydrochloride | 15A12-B03-306306 | 1       |
| Caelo                | Tetracaine hydrochloride | 15H24-B03        | 3       |
| AHD                  | Tetracaine hydrochloride | 15A12-B03-308857 | 1       |
| Fagron               | Tetracaine hydrochloride | 15H24-B03-311450 | 6       |
| Fagron               | Tetracaine hydrochloride | 15H24-B03-313594 | 3       |

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| Supplier                   | Substance                | Batch            | Spectra |
|----------------------------|--------------------------|------------------|---------|
| Fagron                     | Tetracaine hydrochloride | 15K04-B03        | 2       |
| Fagron                     | Tetracaine hydrochloride | 15K04-B03-322151 | 1       |
| Caelo                      | Tetracaine hydrochloride | 15K04-B03-318369 | 1       |
| Fagron                     | Tetracaine hydrochloride | 15K04B03318369   | 1       |
| Fagron                     | Tetracaine hydrochloride | 15K04-bo3-312151 | 1       |
| Ebert-Jacobi               | Tetracaine hydrochloride | 15K04-B03-328163 | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 1607031          | 1       |
| Phoenix 04.11.16 Phoeni... | Tetracaine hydrochloride | 1607031-01       | 1       |
| Caelo                      | Tetracaine hydrochloride | 1607031-01       | 2       |
| Ebert-Jacobi               | Tetracaine hydrochloride | 1612005-01       | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 1612005-01       | 3       |
| Fagron                     | Tetracaine hydrochloride | 16G28-B03        | 1       |
| Fagron                     | Tetracaine hydrochloride | 16G28-B03-327368 | 3       |
| Fagron                     | Tetracaine hydrochloride | 16G28-B03-327369 | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 17081503         | 1       |
| Fagron                     | Tetracaine hydrochloride | 221630-0003      | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 24102014A        | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 4811A-02039      | 1       |
| Caelo                      | Tetracaine hydrochloride | 4827030          | 2       |
| BASF/ Phoenix              | Tetracaine hydrochloride | 6093547          | 1       |
| Orgamol Pharma             | Tetracaine hydrochloride | 6093547          | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 6093547          | 1       |
| Fagron                     | Tetracaine hydrochloride | 10990837         | 2       |
| Caelo                      | Tetracaine hydrochloride | 10118210         | 2       |
| Caelo                      | Tetracaine hydrochloride | 9070003          | 2       |
| Caelo                      | Tetracaine hydrochloride | 10118211         | 1       |
| gehe, 03.01.2013           | Tetracaine hydrochloride | 10118211         | 1       |
| Anzag 19.06.2012           | Tetracaine hydrochloride | 10118218         | 1       |
| Caelo                      | Tetracaine hydrochloride | 10118218         | 1       |
| Caelo                      | Tetracaine hydrochloride | 10118225         | 6       |
| Fagron                     | Tetracaine hydrochloride | 10A29-N12        | 2       |
| Fagron                     | Tetracaine hydrochloride | 11/15-N12        | 2       |
| Noweda                     | Tetracaine hydrochloride | 11/15-N12        | 2       |
| Noweda                     | Tetracaine hydrochloride | 1106035-01       | 2       |
| Euro OTC                   | Tetracaine hydrochloride | 1106035-01       | 1       |
| EuRho                      | Tetracaine hydrochloride | 1106035-01       | 2       |
| Euro OTC                   | Tetracaine hydrochloride | 1110010-01       | 6       |
| Noweda                     | Tetracaine hydrochloride | 1106035-02       | 1       |
| EuRho                      | Tetracaine hydrochloride | 1110010-01       | 2       |
| Caelo                      | Tetracaine hydrochloride | 1110010-01       | 1       |
| Caelo                      | Tetracaine hydrochloride | 1110010-02       | 2       |
| Euro OTC                   | Tetracaine hydrochloride | 1110010-02       | 5       |
| anzag, 14.11.2012          | Tetracaine hydrochloride | 1110010-02       | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 111001002        | 1       |
| Fagron                     | Tetracaine hydrochloride | 11I15-N12        | 1       |
| Fagron                     | Tetracaine hydrochloride | 11G22-N04        | 1       |
| Caelo                      | Tetracaine hydrochloride | 12019802         | 4       |
| Euro OTC                   | Tetracaine hydrochloride | 11110010-02      | 1       |
| Fagron                     | Tetracaine hydrochloride | 11A31-N15        | 1       |
| Sanacorp                   | Tetracaine hydrochloride | 12019803         | 1       |
| Phoenix 26.03.2013         | Tetracaine hydrochloride | 12019809         | 1       |
| Gehe 07.03.2013            | Tetracaine hydrochloride | 12019810         | 2       |
| Caelo                      | Tetracaine hydrochloride | 12019810         | 5       |
| Caelo                      | Tetracaine hydrochloride | 12019812         | 3       |
| Caelo                      | Tetracaine hydrochloride | 12019815         | 1       |
| Caelo                      | Tetracaine hydrochloride | 12019816         | 10      |
| Ichthyol-Gesellschaft/V... | Tetracaine hydrochloride | 12019816         | 2       |
| phönix 14.08.2013          | Tetracaine hydrochloride | 12019816         | 1       |
| Sino Phyto                 | Tetracaine hydrochloride | 12019816         | 1       |
| Gehe 05.11.2013            | Tetracaine hydrochloride | 12019822         | 1       |

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| Supplier                   | Substance                | Batch              | Spectra |
|----------------------------|--------------------------|--------------------|---------|
| Caelo                      | Tetracaine hydrochloride | 12019820           | 1       |
| Noweda                     | Tetracaine hydrochloride | 120700-02          | 1       |
| Fagron                     | Tetracaine hydrochloride | 1207001-01         | 5       |
| Anzag 07.03.13             | Tetracaine hydrochloride | 1207001-01         | 2       |
| Caelo                      | Tetracaine hydrochloride | 1207001-01         | 1       |
| EuRho Anzag                | Tetracaine hydrochloride | 1207001-01         | 1       |
| GEHE                       | Tetracaine hydrochloride | 1207001-01         | 1       |
| Euro CT Phönix             | Tetracaine hydrochloride | 1207001-02         | 1       |
| Fagron                     | Tetracaine hydrochloride | 12C22-N04          | 7       |
| Fagron                     | Tetracaine hydrochloride | 12H24-N05          | 9       |
| Caelo                      | Tetracaine hydrochloride | 12H24-N05          | 5       |
| Noweda                     | Tetracaine hydrochloride | 12H24-N05          | 2       |
| Noweda/ BASF Pharma (Ev... | Tetracaine hydrochloride | 12H24-N05          | 1       |
| Alliance Healthcare        | Tetracaine hydrochloride | 12H24-N05          | 1       |
| Caelo                      | Tetracaine hydrochloride | 12h24-n05          | 1       |
| Noveda                     | Tetracaine hydrochloride | 12H24-N05          | 1       |
| Fagron                     | Tetracaine hydrochloride | 12H24-N050696/1050 | 1       |
| Fagron                     | Tetracaine hydrochloride | 12H-N05            | 1       |
| Fagron                     | Tetracaine hydrochloride | 12K01-N04          | 8       |
| Großhandel                 | Tetracaine hydrochloride | 12K01-N04          | 1       |
| Phönix                     | Tetracaine hydrochloride | 12K01-N04          | 1       |
| gehe                       | Tetracaine hydrochloride | 1303012            | 1       |
| Fagron                     | Tetracaine hydrochloride | 1303012-01         | 1       |
| Phönix                     | Tetracaine hydrochloride | 130301201          | 1       |
| Sanacorp                   | Tetracaine hydrochloride | 1303012-01         | 1       |
| BASF Pharma S.A.           | Tetracaine hydrochloride | 1310006-01         | 1       |
| Caelo                      | Tetracaine hydrochloride | 1310006-01         | 1       |
| Fagron                     | Tetracaine hydrochloride | 13D11-N01          | 1       |
| Phönix                     | Tetracaine hydrochloride | 13155710           | 1       |
| Fagron                     | Tetracaine hydrochloride | 13G02-N01          | 1       |
| Fagron                     | Tetracaine hydrochloride | 13K25-B04290276    | 1       |
| Fagron                     | Tetracaine hydrochloride | 13k25-b04-290276   | 1       |
| Caelo                      | Tetracaine hydrochloride | 27111305           | 1       |
| Fagron                     | Tetracaine hydrochloride | 13q11-n07          | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 20160812-2         | 1       |
| Fagron                     | Tetracaine hydrochloride | 212131/221630-0002 | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 2906009V-03        | 1       |
| Finze                      | Tetracaine hydrochloride | 2906009-02         | 1       |
| EuRho                      | Tetracaine hydrochloride | 2906009V-04        | 1       |
| Fagron                     | Tetracaine hydrochloride | 3413U02039         | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 3113M-02039        | 1       |
| Fagron                     | Tetracaine hydrochloride | 3913I-02039        | 1       |
| Fagron                     | Tetracaine hydrochloride | 4313E-02039        | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 140902601          | 1       |
| Euro OTG Pharma            | Tetracaine hydrochloride | 1409026-02         | 1       |
| Fagron                     | Tetracaine hydrochloride | 14c18-B03-300200   | 1       |
| Caelo                      | Tetracaine hydrochloride | 1303012-01         | 2       |
| Gutenberg-Apotheke         | Tetracaine hydrochloride | 13D11-N07          | 1       |
| Sanacorp, 21.02.17, 13,... | Tetracaine hydrochloride | 1607031-01         | 1       |
| VDI 26.09.14 12,00 euro    | Tetracaine hydrochloride | 1405026-01         | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 14090-26           | 1       |
| Euro OTC                   | Tetracaine hydrochloride | 14G14-B08-300202   | 1       |
| Synopharm/Anzag            | Tetracaine hydrochloride | 2712Q-02039        | 1       |
| Jenne                      | Tetracaine hydrochloride | 13D11-No7          | 1       |

- 69 025 spectra from 414 *Apo-Ident* customers from a total of 23 658 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are docu-



mented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tetracaine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tetracaine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 230           | 0              | 71 156        |
| <b>Type B</b> | 0              | 188           | 37             | 146 504       |
| <b>Type C</b> | 0              | 556           | 52             | 69 025        |

The substance/substance group *Tetracaine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.3913 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 83.5556 % (> 82.2222 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 91.4474 % (> 90.9539 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20924     | 21845               | 6.00                         | 67.40                           |
| 21845     | 21845               | 0.00                         | 65.53                           |
| 22285     | 22285               | 0.00                         | 65.17                           |
| 22912     | 22912               | 0.00                         | 67.58                           |
| 23162     | 22912               | 4.39                         | 67.19                           |
| 23163     | 21845               | 4.80                         | 66.59                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe

von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tetracycline hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20044-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tetracycline hydrochloride; Tetracyclini hydrochloridum; Tetracyclinum hydrochloricum

### Special notes

When selecting the *Tetracycline hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F *Zusatz zu den Modellen der zweiten Stufe*

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tetracycline hydrochloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Euro OTC | Tetracycline hyd... | 1302012-01 | 21079     | 40      | 1411585     |
| Caelo    | Tetracycline hyd... | 13201303   | 21427     | 39      | 20130807    |
| Caelo    | Tetracycline hyd... | 13201303   | 21428     | 40      | 20130807    |
| Euro OTC | Tetracycline hyd... | 1506012    | 21835     | 40      | 20150707*   |
| Caelo    | Tetracycline hyd... | 161167     | 22468     | 40      | 20160504*   |
| Caelo    | Tetracycline hyd... | 15230712   | 22833     | 40      | 20150819    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 239 spectra of 6 reference samples from the substance/substance group *Tetracycline hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 147 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 7 reference samples from the substance/substance group *Tetracycline hydrochloride*.

| Supplier | Substance                  | Batch    | Sample ID          | Spectra |
|----------|----------------------------|----------|--------------------|---------|
| Fagron   | Tetracycline hydrochloride | 9C25-N10 | 20044              | 30      |
| Caelo    | Tetracycline hydrochloride | 13201303 | 21427 <sup>†</sup> | 20      |
| Caelo    | Tetracycline hydrochloride | 13201303 | 21428 <sup>†</sup> | 20      |
| Euro OTC | Tetracycline hydrochloride | 1506012  | 21835 <sup>†</sup> | 20      |
| Caelo    | Tetracycline hydrochloride | 161167   | 22468 <sup>†</sup> | 20      |
| Euro OTC | Tetracycline hydrochloride | 1603026  | 22545              | 40      |
| Euro OTC | Tetracycline hydrochloride | 1706020  | 23691              | 30      |

- 146 549 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 240 spectra from 118 *Apo-Ident* customers from 77 batches from the substance/substance group *Tetracycline hydrochloride*.

| Supplier                   | Substance                  | Batch            | Spectra |
|----------------------------|----------------------------|------------------|---------|
| Caelo                      | Tetracycline hydrochloride | 103201301        | 1       |
| Euro OTC                   | Tetracycline hydrochloride | 1110029-01       | 4       |
| Caelo                      | Tetracycline hydrochloride | 1017A-02378      | 1       |
| Euro OTC                   | Tetracycline hydrochloride | 1204039-02       | 13      |
| EuRho/AHD                  | Tetracycline hydrochloride |                  | 1       |
| Anzag/euRho                | Tetracycline hydrochloride |                  | 1       |
| Caelo                      | Tetracycline hydrochloride | 12353603         | 6       |
| Caelo                      | Tetracycline hydrochloride | 12353616         | 1       |
| Euro OTC                   | Tetracycline hydrochloride | 1302012-01       | 9       |
| Aliance am 10.03.2014      | Tetracycline hydrochloride | 1302012-02       | 1       |
| Euro OTC                   | Tetracycline hydrochloride | 1302012-02       | 18      |
| Caelo                      | Tetracycline hydrochloride | 1302012-02       | 1       |
| Euro OTC                   | Tetracycline hydrochloride | 13042015C        | 1       |
| EuRho                      | Tetracycline hydrochloride | 1302012-02       | 1       |
| Caelo                      | Tetracycline hydrochloride | 13201302         | 3       |
| Fagron                     | Tetracycline hydrochloride | 13201301         | 1       |
| Caelo                      | Tetracycline hydrochloride | 13201301         | 3       |
| Alliance Health 22.08.2... | Tetracycline hydrochloride | 13201307         | 1       |
| Caelo                      | Tetracycline hydrochloride | 13201307         | 1       |
| Celo/Kehr                  | Tetracycline hydrochloride | 13201307         | 1       |
| Caelo                      | Tetracycline hydrochloride | 13201309         | 2       |
| Fagron                     | Tetracycline hydrochloride | 13F17-N03        | 4       |
| Caelo                      | Tetracycline hydrochloride | 13F17-N03        | 1       |
| Fagron                     | Tetracycline hydrochloride | 13J22-N04        | 1       |
| Fagron                     | Tetracycline hydrochloride | 13L10-B02-294454 | 1       |
| Fagron                     | Tetracycline hydrochloride | 13L10-B02-294455 | 2       |
| Phönix/Euro                | Tetracycline hydrochloride | 1402030-01       | 1       |
| Euro OTC                   | Tetracycline hydrochloride | 1402030-01       | 9       |
| Caelo                      | Tetracycline hydrochloride | 13L10B02296956   | 1       |
| Sanacorp                   | Tetracycline hydrochloride | 1402030-01       | 1       |
| EuRho                      | Tetracycline hydrochloride | 1402030-02       | 1       |
| Euro OTC                   | Tetracycline hydrochloride | 1402030-02       | 6       |
| Caelo                      | Tetracycline hydrochloride | 14080605         | 3       |
| Caelo                      | Tetracycline hydrochloride | 14080606         | 2       |
| Fagron                     | Tetracycline hydrochloride | 1402030-02       | 1       |
| Bombastus                  | Tetracycline hydrochloride | 1412007-01       | 1       |
| Euro OTC                   | Tetracycline hydrochloride | 1412007          | 1       |
| Euro OTC                   | Tetracycline hydrochloride | 1412007-01       | 7       |
| Euro OTC                   | Tetracycline hydrochloride | 14120007-01      | 1       |
| Caelo                      | Tetracycline hydrochloride | 1412007-01       | 2       |
| Caelo                      | Tetracycline hydrochloride | 14364601         | 1       |
| Caelo                      | Tetracycline hydrochloride | 14364604         | 3       |
| Hoff/ Noweda               | Tetracycline hydrochloride | 14364604         | 1       |
| Caelo                      | Tetracycline hydrochloride | 14364612         | 2       |
| Caelo                      | Tetracycline hydrochloride | 14364616         | 2       |
| Caelo                      | Tetracycline hydrochloride | 14364617         | 2       |
| Fagron                     | Tetracycline hydrochloride | 14H06-B05        | 2       |
| Fagron                     | Tetracycline hydrochloride | 14H06-B05-303912 | 3       |
| Fagron                     | Tetracycline hydrochloride | 14H06-B05-299498 | 1       |
| Fagron                     | Tetracycline hydrochloride | 14H06-B05-303911 | 1       |
| Fagron                     | Tetracycline hydrochloride | 14H06-B05-311707 | 1       |
| Caelo                      | Tetracycline hydrochloride | 14H06-B05-313591 | 1       |
| Fagron                     | Tetracycline hydrochloride | 14H06-B05-314870 | 1       |
| Euro OTC                   | Tetracycline hydrochloride | 1506012-01       | 22      |

*continued on the next page*

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| Supplier         | Substance                  | Batch            | Spectra |
|------------------|----------------------------|------------------|---------|
| Fagron           | Tetracycline hydrochloride | 14H06-Bo5-303912 | 1       |
| Caelo            | Tetracycline hydrochloride | 1506012-01       | 1       |
| Caelo            | Tetracycline hydrochloride | 15230703         | 1       |
| Gehe             | Tetracycline hydrochloride | 15230703         | 1       |
| Caelo            | Tetracycline hydrochloride | 15230707         | 3       |
| Caelo            | Tetracycline hydrochloride | 15230715         | 2       |
| Caelo            | Tetracycline hydrochloride | 15230717         | 1       |
| Euro OTC         | Tetracycline hydrochloride | 160302601        | 2       |
| Euro OTC         | Tetracycline hydrochloride | 1603026          | 1       |
| Euro OTC         | Tetracycline hydrochloride | 1603026-01       | 10      |
| Caelo            | Tetracycline hydrochloride | 1603026-01       | 3       |
| Bombastus        | Tetracycline hydrochloride | 1603026-01       | 2       |
| Ningxia          | Tetracycline hydrochloride | 1603026-01       | 2       |
| Ichthyol/Phönix  | Tetracycline hydrochloride | 1603026-01       | 1       |
| Euro OTC         | Tetracycline hydrochloride | 21111404         | 1       |
| Caelo            | Tetracycline hydrochloride | 4315I-02378      | 1       |
| Caelo            | Tetracycline hydrochloride | 9248704          | 1       |
| Caelo            | Tetracycline hydrochloride | 2714U-02378      | 1       |
| Caelo            | Tetracycline hydrochloride | 4012Q-02378      | 1       |
| Gehe             | Tetracycline hydrochloride | 16116706         | 1       |
| Euro OTC         | Tetracycline hydrochloride | 100518-62        | 1       |
| Sanacorp         | Tetracycline hydrochloride | 100403401        | 1       |
| Caelo            | Tetracycline hydrochloride | 5091202          | 1       |
| Kehr             | Tetracycline hydrochloride | 1110029-01       | 1       |
| Caelo            | Tetracycline hydrochloride | 111002901        | 1       |
| Gehe             | Tetracycline hydrochloride | 1110029-01       | 1       |
| Euro OTC         | Tetracycline hydrochloride | 12040390         | 1       |
| Caelo            | Tetracycline hydrochloride | 1204039          | 2       |
| Euro OTC         | Tetracycline hydrochloride | 1204039-01       | 5       |
| Europharm/Otto   | Tetracycline hydrochloride | 1204039-02       | 3       |
| Noweda           | Tetracycline hydrochloride | 1204039-01       | 1       |
| Europharm/Otto   | Tetracycline hydrochloride | 1204039-01       | 1       |
| Euro OTC         | Tetracycline hydrochloride | 120403902        | 1       |
| Eurho/Phoenix    | Tetracycline hydrochloride | 1204039-02       | 1       |
| 200, 14.11.2012  | Tetracycline hydrochloride | 12138104         | 1       |
| Caelo            | Tetracycline hydrochloride | 12138104         | 1       |
| Caelo            | Tetracycline hydrochloride | 12138106         | 2       |
| Anzag 30.04.2013 | Tetracycline hydrochloride | 12353602         | 1       |
| Caelo            | Tetracycline hydrochloride | 12353602         | 1       |
| Caelo            | Tetracycline hydrochloride | 12353609         | 1       |
| Caelo            | Tetracycline hydrochloride | 12353612         | 2       |
| Fagron           | Tetracycline hydrochloride | 12E10-N05        | 1       |
| Caelo            | Tetracycline hydrochloride | 1235613          | 1       |
| Fagron           | Tetracycline hydrochloride | 12J15-N05        | 1       |
| Caelo            | Tetracycline hydrochloride | 1302012-01       | 1       |
| Phönix Gotha     | Tetracycline hydrochloride | 1302012-01       | 1       |
| Euro OTC         | Tetracycline hydrochloride | 140410-62        | 1       |
| Euro OTC         | Tetracycline hydrochloride | 141200701        | 1       |
| ningxia          | Tetracycline hydrochloride | 1412007-01       | 1       |
| Euro OTC         | Tetracycline hydrochloride | 150601201        | 1       |
| Euro OTC         | Tetracycline hydrochloride | 28021315         | 1       |
| Caelo            | Tetracycline hydrochloride | 2612Q-02378      | 1       |
| Caelo            | Tetracycline hydrochloride | 1103003-02       | 1       |
| EUro/AHD         | Tetracycline hydrochloride | 1302012-01       | 1       |

- 69 393 spectra from 414 *Apo-Ident* customers from a total of 23 724 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are docu-

mented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tetracycline hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tetracycline hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 239           | 0              | 71 147        |
| <b>Type B</b> | 0              | 160           | 20             | 146 549       |
| <b>Type C</b> | 0              | 224           | 16             | 69 393        |

The substance/substance group *Tetracycline hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.4895 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 88.8889 % (> 87.2222 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 93.3333 % (> 92.0833 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21079     | 21079               | 0.00                         | 27.93                           |
| 21427     | 21835               | 6.32                         | 30.35                           |
| 21428     | 21835               | 2.67                         | 29.89                           |
| 21835     | 21835               | 0.00                         | 29.41                           |
| 22468     | 22468               | 0.00                         | 28.17                           |
| 22833     | 21079               | 5.85                         | 28.73                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe

von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Thalidomide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21552-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Thalidomide; Thalidomidum

### Special notes

When selecting the *Thalidomide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Thalidomide*:

| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate |
|----------|-------------|------------------|-----------|---------|-------------|
| Fagron   | Thalidomide | 14E27B04295348   | 21552     | 40      | 1503608     |
| Caelo    | Thalidomide | 13395704         | 21739     | 40      | 20140207    |
| Caelo    | Thalidomide | 15276711         | 22880     | 40      | 1704508     |
| Fagron   | Thalidomide | 15A13-B01-312230 | 22882     | 40      | 1704509     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Thalidomide*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 4 reference samples from the substance/substance group *Thalidomide*.

| Supplier | Substance   | Batch          | Sample ID          | Spectra |
|----------|-------------|----------------|--------------------|---------|
| Fagron   | Thalidomide | 14E27B04295348 | 21552 <sup>†</sup> | 20      |
| Caelo    | Thalidomide | 13395704       | 21739 <sup>†</sup> | 20      |
| Caelo    | Thalidomide | 162703         | 22774              | 40      |
| Caelo    | Thalidomide | 172100         | 23684              | 40      |

- 146 609 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Thalidomide*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier | Substance   | Batch            | Spectra |
|----------|-------------|------------------|---------|
| Fagron   | Thalidomide | 14E27-B04-299297 | 1       |

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Thalidomide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Thalidomide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 120           | 0              | 146 609       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Thalidomide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21552     | 21552               | 0.00                         | 54.59                           |
| 21739     | 21552               | 16.69                        | 57.05                           |
| 22880     | 22880               | 0.00                         | 56.47                           |
| 22882     | 22882               | 0.00                         | 57.51                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Theophylline**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20723-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Theophylline; Theophyllinum

### Special notes

When selecting the *Theophylline* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Theophylline*:

| Supplier | Substance    | Batch    | Sample ID | Spectra | Certificate |
|----------|--------------|----------|-----------|---------|-------------|
| Caelo    | Theophylline | 12166316 | 20723     | 40      | 1402055     |
| Caelo    | Theophylline | 12341101 | 21740     | 40      | 20121115    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Theophylline*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *Theophylline*.

| Supplier | Substance    | Batch    | Sample ID          | Spectra |
|----------|--------------|----------|--------------------|---------|
| Caelo    | Theophylline | 12341101 | 21740 <sup>†</sup> | 20      |
| Caelo    | Theophylline | 15203018 | 23253              | 40      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 12 spectra from 11 *Apo-Ident* customers from 8 batches from the substance/substance group *Theophylline*.

| Supplier | Substance    | Batch    | Spectra |
|----------|--------------|----------|---------|
| Caelo    | Theophylline | 12341101 | 2       |
| Caelo    | Theophylline | 12341104 | 1       |
| Caelo    | Theophylline | 12166305 | 2       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier              | Substance    | Batch       | Spectra |
|-----------------------|--------------|-------------|---------|
| Noweda                | Theophylline | 12166305    | 1       |
| Caelo                 | Theophylline | 12166306    | 1       |
| Caelo                 | Theophylline | 12166312    | 1       |
| Caesar&lorenz,Phoenix | Theophylline | 12166315    | 1       |
| Caelo                 | Theophylline | 12166315    | 1       |
| Caelo                 | Theophylline | 12166311    | 1       |
| Caelo                 | Theophylline | 3912A-02382 | 1       |

- 69 621 spectra from 414 *Apo-Ident* customers from a total of 23 793 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Theophylline* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Theophylline* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 12            | 0              | 69 621        |

The substance/substance group *Theophylline* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20723     | 20723               | 0.00                         | 81.90                           |
| 21740     | 20723               | 7.67                         | 78.87                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

|                                     |                                                                 |
|-------------------------------------|-----------------------------------------------------------------|
| Validated substance/substance group | <b>Theophylline-ethylenediamine hydrate</b>                     |
| Substance class                     | APIs & excipients, solid                                        |
| Report date                         | 19/01/2018                                                      |
| Report number                       | 20831-2018-01-19                                                |
| Executing company                   | HiperScan GmbH<br>Weißeritzstraße 3<br>01067 Dresden<br>Germany |

### Relevant substance names

Theophylline-ethylenediamine hydrate; Theophyllum aethylendiaminum hydricum; Theophyllum et ethylenediaminum hydricum

### Special notes

When selecting the *Theophylline-ethylenediamine hydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| 978-3-7692-5416-7 | <i>European Pharmacopoeia 8th Edition, Basic Version 2014</i> [3] |
| Komm2.2.40        | <i>Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident</i> [4]          |
| AA004             | <i>Erstellung und Validierung eines IdentModul-Updates</i>        |
| Anhang F          | <a href="#">Zusatz zu den Modellen der zweiten Stufe</a>          |

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Theophylline-ethylenediamine hydrate*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Theophylline-eth... | 12145301 | 20831     | 40      | 20120628    |
| Caelo    | Theophylline-eth... | 12363708 | 20992     | 40      | 20130116    |
| Caelo    | Theophylline-eth... | 13268609 | 21549     | 40      | 1412133     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Theophylline-ethylenediamine hydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 70 spectra of 2 reference samples from the substance/substance group *Theophylline-ethylenediamine hydrate*.

| Supplier | Substance                       | Batch    | Sample ID | Spectra |
|----------|---------------------------------|----------|-----------|---------|
| Caelo    | Theophylline-ethylenediamine... | 15380302 | 22589     | 40      |
| Caelo    | Theophylline-ethylenediamine... | 17073707 | 23564     | 30      |

- 146 659 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Theophylline-ethylenediamine hydrate*.

| Supplier      | Substance                       | Batch      | Spectra |
|---------------|---------------------------------|------------|---------|
| ACM / Phoenix | Theophylline-ethylenediamine... | KNC0896J14 | 1       |



- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Theophylline-ethylenediamine hydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Theophylline-ethylenediamine hydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 67            | 3              | 146 659       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Theophylline-ethylenediamine hydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 95.7143 % (> 91.4286 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20831     | 21549               | 5.26                         | 60.04                           |
| 20992     | 21549               | 3.91                         | 57.33                           |
| 21549     | 21549               | 0.00                         | 57.67                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das

alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Thiamine chloride hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20566-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Thiamine chloride hydrochloride; Aneurinum hydrochloricum; Thiamini hydrochloridum

### Special notes

When selecting the *Thiamine chloride hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Thiamine chloride hydrochloride*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------------|------------|-----------|---------|-------------|
| Caelo    | Thiamine chlorid... | 14069502   | 21511     | 40      | 8986        |
| Euro OTC | Thiamine chlorid... | 1211008-02 | 21647     | 40      | 20121122    |
| Caelo    | Thiamine chlorid... | 160156     | 22477     | 40      | 20160316*   |
| Euro OTC | Thiamine chlorid... | 1612004    | 22919     | 40      | 20170117*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Thiamine chloride hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 480 spectra of 13 reference samples from the substance/substance group *Thiamine chloride hydrochloride*.

| Supplier | Substance                       | Batch      | Sample ID          | Spectra |
|----------|---------------------------------|------------|--------------------|---------|
| Fagron   | Thiamine chloride hydrochlor... | L11030345  | 20386              | 40      |
| Euro OTC | Thiamine chloride hydrochlor... | 1106001-01 | 20406              | 40      |
| Euro OTC | Thiamine chloride hydrochlor... | 1008026    | 20529              | 40      |
| Euro OTC | Thiamine chloride hydrochlor... | 1106001-01 | 20533              | 40      |
| Caelo    | Thiamine chloride hydrochlor... | 10316406   | 20538              | 40      |
| Fagron   | Thiamine chloride hydrochlor... | 12D16-N02  | 20566              | 40      |
| Caelo    | Thiamine chloride hydrochlor... | 11371302   | 20570              | 40      |
| Caelo    | Thiamine chloride hydrochlor... | 14069502   | 21478              | 60      |
| Caelo    | Thiamine chloride hydrochlor... | 14069502   | 21511 <sup>†</sup> | 20      |
| Euro OTC | Thiamine chloride hydrochlor... | 1211008-02 | 21647 <sup>†</sup> | 20      |
| Caelo    | Thiamine chloride hydrochlor... | 160156     | 22477 <sup>†</sup> | 20      |
| Caelo    | Thiamine chloride hydrochlor... | 170976     | 23368              | 40      |
| Euro OTC | Thiamine chloride hydrochlor... | 1705034    | 23439              | 40      |

- 146 249 spectra from a total of 3183 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 31 spectra from 13 *Apo-Ident* customers from 23 batches from the substance/substance group *Thiamine chloride hydrochloride*.

| Supplier | Substance                       | Batch       | Spectra |
|----------|---------------------------------|-------------|---------|
| Caelo    | Thiamine chloride hydrochlor... | 11371309    | 2       |
| Caelo    | Thiamine chloride hydrochlor... | 4071402     | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 8121405     | 1       |
| Fagron   | Thiamine chloride hydrochlor... | 10111401    | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 11061401    | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 12091407    | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 12340712    | 1       |
| Sanacorp | Thiamine chloride hydrochlor... | 12340712    | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 13296610    | 4       |
| Fagron   | Thiamine chloride hydrochlor... | 13E22-No8   | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 14069502    | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 15003201    | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 15199009    | 2       |
| Fagron   | Thiamine chloride hydrochlor... | 190115006   | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 15199099    | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 5122        | 1       |
| Euro OTC | Thiamine chloride hydrochlor... | 1106001-01  | 1       |
| Finze    | Thiamine chloride hydrochlor... | 9216114     | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 11371313    | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 11371319    | 3       |
| Euro OTC | Thiamine chloride hydrochlor... | 1211008-01  | 1       |
| Caelo    | Thiamine chloride hydrochlor... | 3312A-01119 | 1       |
| Euro OTC | Thiamine chloride hydrochlor... | L1305038-01 | 1       |
| Caelo    | Thiamine chloride hydrochlor... |             | 1       |

- 69 602 spectra from 414 *Apo-Ident* customers from a total of 23 779 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Thiamine chloride hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Thiamine chloride hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 400           | 80             | 146 249       |
| <b>Type C</b> | 0              | 28            | 3              | 69 602        |

The substance/substance group *Thiamine chloride hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 83.3333 % (> 82.7083 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 90.3226 % (> 80.6452 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21511            | 21511                      | 0.00                                | 43.58                                  |
| 21647            | 22477                      | 12.13                               | 41.41                                  |
| 22477            | 22477                      | 0.00                                | 36.04                                  |
| 22919            | 22919                      | 0.00                                | 41.42                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Thymol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20003-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Thymol; Thymolum

### Special notes

When selecting the *Thymol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Thymol*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Caelo    | Thymol    | 14025805   | 21469     | 40      | 20140127    |
| Euro OTC | Thymol    | 1312022-02 | 21639     | 40      | 20131219    |
| Euro OTC | Thymol    | 1510004    | 21943     | 40      | 20151016*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Thymol*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 170 spectra of 6 reference samples from the substance/substance group *Thymol*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Caelo    | Thymol    | 82563169         | 20003              | 30      |
| Caelo    | Thymol    | 14025805         | 21469 <sup>†</sup> | 20      |
| Euro OTC | Thymol    | 1312022-02       | 21639 <sup>†</sup> | 20      |
| Euro OTC | Thymol    | 1510004          | 21943 <sup>†</sup> | 20      |
| Caelo    | Thymol    | 16144101         | 23160              | 40      |
| Fagron   | Thymol    | 15H13-B05-328912 | 23499              | 40      |

- 146 559 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 69 spectra from 55 *Apo-Ident* customers from 40 batches from the substance/substance group *Thymol*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier                | Substance | Batch      | Spectra |
|-------------------------|-----------|------------|---------|
| Sanacorp                | Thymol    | 9E14-N16   | 1       |
| Caelo                   | Thymol    | 11178718   | 1       |
| Caelo                   | Thymol    | 11178716   | 1       |
| Caelo                   | Thymol    | 2031503    | 1       |
| Caelo                   | Thymol    | 11358607   | 3       |
| Sanacorp                | Thymol    | 1135816    | 1       |
| Caelo                   | Thymol    | 11358608   | 1       |
| Phönix                  | Thymol    | 11358610   | 1       |
| Caelo                   | Thymol    | 11358616   | 2       |
| Caelo                   | Thymol    | 11358610   | 1       |
| Euro OTC                | Thymol    | 1202028-01 | 2       |
| Fagron                  | Thymol    | 12B06-N11  | 2       |
| Fagron                  | Thymol    | 12D04-N04  | 1       |
| Fagron                  | Thymol    | 12H29-N02  | 3       |
| Fagron                  | Thymol    | 12E30-N11  | 1       |
| Fagron                  | Thymol    | 12K01-N02  | 3       |
| Frey+Lau GmbH/Phönix    | Thymol    | 1312022-01 | 1       |
| Fagron                  | Thymol    | 12M29-N02  | 1       |
| Euro OTC                | Thymol    | 1312022-01 | 1       |
| Noweda                  | Thymol    | 12k01-no2  | 1       |
| Gehe Kassel             | Thymol    | 1312022-01 | 1       |
| Caelo                   | Thymol    | 13288802   | 4       |
| Caelo                   | Thymol    | 13147502   | 2       |
| Caesar § Lorenz GmbH    | Thymol    | 13288806   | 1       |
| PHOENIX 26.03.2014      | Thymol    | 14025802   | 2       |
| Caelo                   | Thymol    | 14025802   | 2       |
| Caelo                   | Thymol    | 14025805   | 1       |
| Caelo                   | Thymol    | 14025809   | 2       |
| Caelo                   | Thymol    | 14025815   | 2       |
| Euro OTC                | Thymol    | 1410007-01 | 4       |
| Caelo                   | Thymol    | 14025816   | 1       |
| Caelo                   | Thymol    | 14302401   | 1       |
| Caelo                   | Thymol    | 14310601   | 1       |
| Caelo                   | Thymol    | 14310605   | 1       |
| Euro OTC                | Thymol    | 1510004-01 | 1       |
| Phönix                  | Thymol    | 1510004-01 | 1       |
| Caelo                   | Thymol    | 15130106   | 1       |
| Euro OTC                | Thymol    | 1510004-02 | 3       |
| Caelo                   | Thymol    | 15362901   | 2       |
| Caelo                   | Thymol    | 15130101   | 1       |
| Ebert & Jacobi 02.08... | Thymol    | 15362901   | 1       |
| Caelo                   | Thymol    | 15362908   | 1       |
| Caelo                   | Thymol    | 19061303   | 1       |
| Euro OTC                | Thymol    | 20151012-1 | 1       |
| Fagron                  | Thymol    | 713575     | 1       |
| ACM / Herba             | Thymol    | KNC1166J14 | 1       |

- 69 564 spectra from 414 *Apo-Ident* customers from a total of 23 761 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Thymol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all

relevant spectra of the various substances were compared with *Thymol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 169           | 1              | 146 559       |
| <b>Type C</b> | 0              | 67            | 2              | 69 564        |

The substance/substance group *Thymol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.4118 % (> 97.6471 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 97.1014 % (> 92.7536 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21469     | 21943               | 15.34                        | 47.87                           |
| 21639     | 21943               | 21.67                        | 50.26                           |
| 21943     | 21943               | 0.00                         | 55.62                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tobramycin sulfate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20951-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tobramycin sulfate; Tobramycin sulphate; Tobramycini sulfas; Tobramycinum sulfuricum

### Special notes

When selecting the *Tobramycin sulfate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tobramycin sulfate*:

| Supplier | Substance          | Batch            | Sample ID | Spectra | Certificate |
|----------|--------------------|------------------|-----------|---------|-------------|
| Fagron   | Tobramycin sulfate | 12G03-N03        | 20951     | 40      | 1404541     |
| Euro OTC | Tobramycin sulfate | 1301011-02       | 21624     | 40      | 1508071     |
| Euro OTC | Tobramycin sulfate | 1505015-01       | 21832     | 40      | 8963        |
| Euro OTC | Tobramycin sulfate | 1510035-01       | 22240     | 40      | 9202        |
| Euro OTC | Tobramycin sulfate | 1510035          | 22252     | 40      | 20151208*   |
| Fagron   | Tobramycin sulfate | 15I17-B04-315697 | 22359     | 30      | pending     |
| Audor    | Tobramycin sulfate | AP15061047002T   | 22393     | 40      | 1608462     |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 270 spectra of 7 reference samples from the substance/substance group *Tobramycin sulfate*. These samples are listed above in the [calibration samples](#) section.
- 71 116 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 355 spectra of 10 reference samples from the substance/substance group *Tobramycin sulfate*.

| Supplier     | Substance          | Batch            | Sample ID          | Spectra |
|--------------|--------------------|------------------|--------------------|---------|
| Euro OTC     | Tobramycin sulfate | 1301011-02       | 21624 <sup>†</sup> | 20      |
| Euro OTC     | Tobramycin sulfate | 1505015-01       | 21832 <sup>†</sup> | 20      |
| Euro OTC     | Tobramycin sulfate | 1510035-01       | 22240 <sup>†</sup> | 20      |
| Euro OTC     | Tobramycin sulfate | 1510035          | 22252 <sup>†</sup> | 20      |
| Fagron       | Tobramycin sulfate | 15I17-B04-315697 | 22359 <sup>†</sup> | 15      |
| Audor Pharma | Tobramycin sulfate | AP15061047002T   | 23502              | 40      |
| Fagron       | Tobramycin sulfate | 16B05-B03-336397 | 23515              | 40      |
| Euro OTC     | Tobramycin sulfate | 1505015-01       | 21832SI            | 60      |
| Euro OTC     | Tobramycin sulfate | 1510035-01       | 22240SI            | 60      |
| Euro OTC     | Tobramycin sulfate | 1510035          | 22252SI            | 60      |

- 146 374 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 11 spectra from 6 *Apo-Ident* customers from 9 batches from the substance/substance group *Tobramycin sulfate*.

| Supplier           | Substance          | Batch            | Spectra |
|--------------------|--------------------|------------------|---------|
| PHOENIX 31.01.2014 | Tobramycin sulfate | 1202006-01       | 1       |
| Fagron             | Tobramycin sulfate | 15/17-B04-315697 | 1       |
| Fagron             | Tobramycin sulfate | 13H09-N09        | 1       |
| Euro OTC           | Tobramycin sulfate | 1505015-01       | 1       |
| Euro OTC           | Tobramycin sulfate | 15I17-B04-315697 | 1       |
| Euro OCT/Noweda    | Tobramycin sulfate | 1510035-01       | 1       |
| Fagron             | Tobramycin sulfate | 16B05-B03        | 2       |
| Fagron             | Tobramycin sulfate | 16B05-B03-317988 | 2       |
| Fagron             | Tobramycin sulfate | 16C04-B06        | 1       |

- 69 622 spectra from 414 *Apo-Ident* customers from a total of 23 792 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tobramycin sulfate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tobramycin sulfate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 270           | 0              | 71 116        |
| <b>Type B</b> | 0              | 301           | 54             | 146 374       |
| <b>Type C</b> | 0              | 9             | 2              | 69 622        |

The substance/substance group *Tobramycin sulfate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.7778 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 84.7887 % (> 83.9437 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20951     | 20951               | 0.00                         | 10.88                           |
| 21624     | 21624               | 0.00                         | 15.38                           |
| 21832     | 21832               | 0.00                         | 18.56                           |
| 22240     | 22240               | 0.00                         | 36.53                           |
| 22252     | 22252               | 0.00                         | 18.12                           |
| 22359     | 22359               | 0.00                         | 20.48                           |
| 22393     | 22393               | 0.00                         | 9.73                            |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tosylchloramide sodium**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20133-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tosylchloramide sodium; Chloraminum; Tosylchloramidum natricum

### Special notes

When selecting the *Tosylchloramide sodium* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tosylchloramide sodium*:

| Supplier | Substance           | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------------|----------|-----------|---------|-------------|
| Caelo    | Tosylchloramide ... | 13103201 | 20864     | 40      | 20130424    |
| Caelo    | Tosylchloramide ... | 13361602 | 21115     | 40      | 1407634     |
| Caelo    | Tosylchloramide ... | 16236603 | 23562     | 40      | 20160819    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Tosylchloramide sodium*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 3 reference samples from the substance/substance group *Tosylchloramide sodium*.

| Supplier | Substance              | Batch    | Sample ID | Spectra |
|----------|------------------------|----------|-----------|---------|
| Caelo    | Tosylchloramide sodium | 9359512  | 20133     | 40      |
| Caelo    | Tosylchloramide sodium | 13361606 | 21480     | 60      |
| Caelo    | Tosylchloramide sodium | 162366   | 22773     | 40      |

- 146 589 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 76 spectra from 32 *Apo-Ident* customers from 39 batches from the substance/substance group *Tosylchloramide sodium*.

| Supplier | Substance              | Batch    | Spectra |
|----------|------------------------|----------|---------|
| Caelo    | Tosylchloramide sodium | 13103206 | 8       |
| Caelo    | Tosylchloramide sodium | 13103210 | 4       |
| Caelo    | Tosylchloramide sodium | 13103207 | 3       |
| Caelo    | Tosylchloramide sodium | 13361606 | 4       |
| Caelo    | Tosylchloramide sodium | 13361607 | 5       |

*continued on the next page*



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| Supplier                | Substance              | Batch            | Spectra |
|-------------------------|------------------------|------------------|---------|
| Caelo                   | Tosylchloramide sodium | 13361608         | 2       |
| Caelo                   | Tosylchloramide sodium | 14183505         | 1       |
| Phoenix goettin         | Tosylchloramide sodium | 14183509         | 1       |
| Caelo                   | Tosylchloramide sodium | 14183509         | 1       |
| Euro OTC                | Tosylchloramide sodium | 14B27-B03-29401  | 1       |
| Fagron                  | Tosylchloramide sodium | 14B27-B3-294701  | 1       |
| Caelo                   | Tosylchloramide sodium | 15039603         | 3       |
| Caelo                   | Tosylchloramide sodium | 15370501         | 3       |
| Caelo                   | Tosylchloramide sodium | 15370505         | 1       |
| Caelo                   | Tosylchloramide sodium | 71051187         | 2       |
| Fagron                  | Tosylchloramide sodium | 181970-003       | 1       |
| Caelo                   | Tosylchloramide sodium | 16236603         | 1       |
| Caelo                   | Tosylchloramide sodium | 72215377         | 2       |
| Caelo                   | Tosylchloramide sodium | 11116709         | 1       |
| Caelo                   | Tosylchloramide sodium | 11/07-N06        | 1       |
| Caelo                   | Tosylchloramide sodium | 11210803         | 1       |
| Caelo                   | Tosylchloramide sodium | 11116708         | 1       |
| Fagron                  | Tosylchloramide sodium | 11L08-N04        | 1       |
| Fagron                  | Tosylchloramide sodium | 11J07-N06        | 1       |
| Fagron                  | Tosylchloramide sodium | 11D19-N05        | 1       |
| Fagron                  | Tosylchloramide sodium | 11L08-N04        | 1       |
| Fagron                  | Tosylchloramide sodium | 12/22-B02-288834 | 1       |
| Caelo                   | Tosylchloramide sodium | 12277005         | 3       |
| Caelo                   | Tosylchloramide sodium | 12323605         | 2       |
| Caelo                   | Tosylchloramide sodium | 12323601         | 1       |
| Caelo                   | Tosylchloramide sodium | 12323606         | 1       |
| Synopharm am 10.09.2012 | Tosylchloramide sodium | 12323607         | 1       |
| Caelo                   | Tosylchloramide sodium | 12323607         | 2       |
| Caelo                   | Tosylchloramide sodium | 12323608         | 1       |
| Caelo                   | Tosylchloramide sodium | 12323609         | 2       |
| Sanacorp                | Tosylchloramide sodium | 12H09-N01        | 1       |
| Anzag                   | Tosylchloramide sodium | 12H09-N01        | 1       |
| Caelo                   | Tosylchloramide sodium | 13103201         | 2       |
| Caelo                   | Tosylchloramide sodium | 13103202         | 1       |
| PHOENIX am 12.06.2012   | Tosylchloramide sodium | 181970-0001      | 1       |
| Fagron                  | Tosylchloramide sodium | Ch12H09-N01      | 2       |
| Fagron                  | Tosylchloramide sodium | 12H09-N01        | 1       |
| Caelo                   | Tosylchloramide sodium | 1310206          | 1       |

- 69 557 spectra from 414 *Apo-Ident* customers from a total of 23 762 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tosylchloramide sodium* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tosylchloramide sodium* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 120           | 0              | 71 266        |
| Type B | 0              | 129           | 11             | 146 589       |
| Type C | 0              | 68            | 8              | 69 557        |

The substance/substance group *Tosylchloramide sodium* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 92.1429 % (> 90.0000 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 89.4737 % (> 85.5263 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20864     | 21115               | 10.21                        | 28.32                           |
| 21115     | 21115               | 0.00                         | 31.06                           |
| 23562     | 21115               | 6.07                         | 31.36                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tranexamic acid**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20397-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tranexamic acid; Acidum tranexamicum

### Special notes

When selecting the *Tranexamic acid* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tranexamic acid*:

| Supplier | Substance       | Batch             | Sample ID | Spectra | Certificate        |
|----------|-----------------|-------------------|-----------|---------|--------------------|
| Fagron   | Tranexamic acid | 14C21-B08-292225  | 21654     | 40      | AR-17-FG-016394-01 |
| Fagron   | Tranexamic acid | 14L15-B06-3000036 | 21727     | 40      | AR-15-FG-008937-02 |
| Fagron   | Tranexamic acid | 16E31-B07-331591  | 23505     | 40      | 20160622           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Tranexamic acid*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 170 spectra of 5 reference samples from the substance/substance group *Tranexamic acid*.

| Supplier     | Substance       | Batch             | Sample ID          | Spectra |
|--------------|-----------------|-------------------|--------------------|---------|
| Fagron       | Tranexamic acid | 11J11-N05         | 20397              | 40      |
| Fagron       | Tranexamic acid | 14C21-B08-292225  | 21654 <sup>†</sup> | 20      |
| Fagron       | Tranexamic acid | 14L15-B06-3000036 | 21727 <sup>†</sup> | 20      |
| Fagron       | Tranexamic acid | 16E31-B07-331591  | 23503              | 50      |
| Audor Pharma | Tranexamic acid | APX1508016MT      | 23504              | 40      |

- 146 559 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 11 spectra from 9 *Apo-Ident* customers from 10 batches from the substance/substance group *Tranexamic acid*.

| Supplier | Substance       | Batch     | Spectra |
|----------|-----------------|-----------|---------|
| Fagron   | Tranexamic acid | 13D08-N24 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier     | Substance       | Batch            | Spectra |
|--------------|-----------------|------------------|---------|
| Fagron       | Tranexamic acid | 13Do8-N24        | 1       |
| Fagron       | Tranexamic acid | 13K08-B04-287966 | 1       |
| Fagron       | Tranexamic acid | 15J29-B04        | 1       |
| Fagron       | Tranexamic acid | 13D08-N240002/40 | 1       |
| Audor Pharma | Tranexamic acid | 1508016MT        | 1       |
| Fagron       | Tranexamic acid | 15J29-B04-312372 | 1       |
| Caelo        | Tranexamic acid | 15J29-B04        | 1       |
| Caelo        | Tranexamic acid | 20110429         | 1       |
| Fagron       | Tranexamic acid | 13G24-N21        | 1       |
| Fagron       | Tranexamic acid | 12D11-N02        | 1       |

- 69 622 spectra from 414 *Apo-Ident* customers from a total of 23 792 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tranexamic acid* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tranexamic acid* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 170           | 0              | 146 559       |
| <b>Type C</b> | 0              | 11            | 0              | 69 622        |

The substance/substance group *Tranexamic acid* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 96.4706 %) |
| <b>Type C</b> | 100.0000 % (> 99.8814 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21654     | 21654               | 0.00                         | 79.89                           |
| 21727     | 21727               | 0.00                         | 84.94                           |
| 23505     | 21654               | 2.29                         | 80.75                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tretinoin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20474-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tretinoin; Tretinoinum

### Special notes

When selecting the *Tretinoin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tretinoin*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Euro OTC | Tretinoin | 1402007-02 | 21747     | 40      | 1507085     |
| Caelo    | Tretinoin | 15028403   | 21757     | 40      | 1507086     |
| Caelo    | Tretinoin | 15239503   | 21878     | 20      | 20150717    |
| Euro OTC | Tretinoin | 1510007    | 21940     | 40      | 20151102*   |
| Euro OTC | Tretinoin | 1604059    | 22574     | 40      | 20160603*   |

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| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Fagron   | Tretinoin | 15F01-B06-317884 | 22936     | 40      | 20150619    |
| Euro OTC | Tretinoin | 1402007-02       | 21747SI   | 40      | 1507085     |
| Caelo    | Tretinoin | 15028403         | 21757SI   | 40      | 1507086     |
| Caelo    | Tretinoin | 15239503         | 21878SI   | 40      | 20150717    |
| Euro OTC | Tretinoin | 1510007          | 21940SI   | 40      | 20151102*   |
| Fagron   | Tretinoin | 15F01-B06-317884 | 22936SI   | 40      | 20150619    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 420 spectra of 11 reference samples from the substance/substance group *Tretinoin*. These samples are listed above in the [calibration samples](#) section.
- 70 966 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 701 spectra of 21 reference samples from the substance/substance group *Tretinoin*.

| Supplier    | Substance | Batch      | Sample ID            | Spectra |
|-------------|-----------|------------|----------------------|---------|
| Caelo       | Tretinoin | 9364503    | 20195                | 41      |
| zu erfassen | Tretinoin | pending    | 20220                | 40      |
| Fagron      | Tretinoin | 11A27-N01  | 20239                | 40      |
| Caelo       | Tretinoin | 11284703   | 20474                | 40      |
| Euro OTC    | Tretinoin | 1402007-02 | 21747 <sup>†</sup>   | 20      |
| Caelo       | Tretinoin | 15028403   | 21757 <sup>†</sup>   | 20      |
| Caelo       | Tretinoin | 15239503   | 21878 <sup>†</sup>   | 40      |
| Euro OTC    | Tretinoin | 1510007    | 21940 <sup>†</sup>   | 20      |
| Caelo       | Tretinoin | 162915     | 22779                | 40      |
| Caelo       | Tretinoin | 162171     | 22780                | 40      |
| Euro OTC    | Tretinoin | 1612010    | 22911                | 40      |
| Caelo       | Tretinoin | 172731     | 23680                | 40      |
| Euro OTC    | Tretinoin | 1402007-02 | 21747SI <sup>†</sup> | 20      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.



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| Supplier | Substance | Batch    | Sample ID            | Spectra |
|----------|-----------|----------|----------------------|---------|
| Caelo    | Tretinoin | 15028403 | 21757SI <sup>†</sup> | 20      |
| Caelo    | Tretinoin | 15239503 | 21878SI <sup>†</sup> | 20      |
| Euro OTC | Tretinoin | 1510007  | 21940SI <sup>†</sup> | 20      |
| Euro OTC | Tretinoin | 1604059  | 22574SI              | 40      |
| Caelo    | Tretinoin | 162915   | 22779SI              | 40      |
| Caelo    | Tretinoin | 162171   | 22780SI              | 40      |
| Euro OTC | Tretinoin | 1612010  | 22911SI              | 40      |
| Caelo    | Tretinoin | 172731   | 23680SI              | 40      |

- 146 028 spectra from a total of 3182 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 352 spectra from 171 *Apo-Ident* customers from 133 batches from the substance/substance group *Tretinoin*.

| Supplier       | Substance | Batch            | Spectra |
|----------------|-----------|------------------|---------|
| Euro OTC       | Tretinoin | 12959AX20        | 2       |
| EuRho/Sanacorp | Tretinoin | 130402802        | 1       |
| Euro OTC       | Tretinoin | 1304028-02       | 6       |
| Nachprüfung    | Tretinoin |                  | 1       |
| Caelo          | Tretinoin | 13278102         | 6       |
| Caelo          | Tretinoin | 13308004         | 5       |
| Fagron         | Tretinoin | 13A08-N07        | 2       |
| Sanacorp       | Tretinoin | 13308004         | 1       |
| Caelo          | Tretinoin | 13B05-B02-287360 | 1       |
| Fagron         | Tretinoin | 13B05-B02-287361 | 2       |
| Fagron         | Tretinoin | 13B05-B02-287360 | 6       |
| Fagron         | Tretinoin | 13C11-N06        | 2       |
| Fagron         | Tretinoin | 13D30N14         | 1       |
| Euro OTC       | Tretinoin | 14020007-01      | 1       |
| Euro OTC       | Tretinoin | 1402007          | 1       |
| Fagron         | Tretinoin | 13D30-N14        | 2       |
| Euro OTC       | Tretinoin | 140200701        | 1       |
| Euro OTC       | Tretinoin | 1402007-01       | 5       |
| Euro OTC       | Tretinoin | 1402007-02       | 7       |
| Fargron        | Tretinoin | 1402007-01       | 1       |
| Phönix         | Tretinoin | 1402007-02       | 1       |
| Euro OTC       | Tretinoin | 1402007-03       | 4       |
| Bombastus      | Tretinoin | 1402007-03       | 1       |
| Caelo          | Tretinoin | 14040504         | 6       |
| Fagron         | Tretinoin | 14040504         | 1       |
| BASF           | Tretinoin | 1402007-03       | 1       |
| Caelo          | Tretinoin | 14093502         | 4       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| <b>Supplier</b>     | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|---------------------|------------------|------------------|----------------|
| Caelo               | Tretinoin        | 14093503         | 2              |
| Fagron              | Tretinoin        | 14093505         | 1              |
| Euro OTC            | Tretinoin        | 14101602         | 1              |
| Sanacorp            | Tretinoin        | 1411016-01       | 1              |
| Euro OTC            | Tretinoin        | 1411016-01       | 10             |
| Caelo               | Tretinoin        | 1411016-01       | 1              |
| Fagron              | Tretinoin        | 1411016-01       | 1              |
| Euro OTC            | Tretinoin        | 141101602        | 1              |
| Sanacorp            | Tretinoin        | 1411016-02       | 1              |
| Euro OTC            | Tretinoin        | 1411016-02       | 8              |
| Eurimpharm          | Tretinoin        | 1411016-01       | 1              |
| Euro                | Tretinoin        | 14111016-01      | 1              |
| Euro OTC            | Tretinoin        | 141107602        | 1              |
| Caelo               | Tretinoin        | 14252702         | 3              |
| Caelo               | Tretinoin        | 14252706         | 2              |
| Caelo               | Tretinoin        | 14252801         | 2              |
| Caelo               | Tretinoin        | 14252710         | 2              |
| Fagron              | Tretinoin        | 14D09-B04        | 1              |
| Phönix              | Tretinoin        | 14D09-B04        | 2              |
| Fagron              | Tretinoin        | 14D09-B04-293594 | 1              |
| Fargron             | Tretinoin        | 14D09-B04-293225 | 1              |
| Fagron              | Tretinoin        | 14D09-B04-293225 | 1              |
| Phönix              | Tretinoin        | 14D09-B04-293224 | 1              |
| Fagron              | Tretinoin        | 14D09-B04-293224 | 1              |
| Fagron              | Tretinoin        | 14D09-B04-295551 | 1              |
| Fagron              | Tretinoin        | 14L24-B01        | 1              |
| Caelo               | Tretinoin        | 14L24-B01-303157 | 1              |
| Fagron              | Tretinoin        | 14L24-B01-303157 | 2              |
| Caelo               | Tretinoin        | 15078301         | 1              |
| Caelo               | Tretinoin        | 15078302         | 2              |
| Anzag/Henry Lamotte | Tretinoin        | 15078303         | 1              |
| Caelo               | Tretinoin        | 15078303         | 2              |
| Caelo               | Tretinoin        | 15078307         | 3              |
| Caelo               | Tretinoin        | 15078305         | 1              |
| Euro OTC            | Tretinoin        | 1510007-01       | 8              |
| Caelo               | Tretinoin        | 15078308         | 1              |
| Caelo               | Tretinoin        | 1510007-01       | 1              |
| Caelo               | Tretinoin        | 151000701        | 1              |
| Euro OTC            | Tretinoin        | 1510007-02       | 6              |
| Caelo               | Tretinoin        | 1510007-02       | 1              |
| Caelo               | Tretinoin        | 15239501         | 1              |
| Caelo               | Tretinoin        | 15239502         | 5              |
| Celo                | Tretinoin        | 15437303         | 1              |
| Caelo               | Tretinoin        | 15239503         | 2              |
| Fagron              | Tretinoin        | 15F01-B06-308722 | 1              |
| Caelo               | Tretinoin        | 15437303         | 4              |
| Sanacorp            | Tretinoin        | 15F01-B06-308722 | 1              |
| Fagron              | Tretinoin        | 15F01-B06-308856 | 1              |
| Fagron              | Tretinoin        | 15F01-B06-313216 | 1              |
| Euro OTC            | Tretinoin        | 1604059-01       | 5              |
| Noweda              | Tretinoin        | 15F01-B06-315491 | 1              |
| Fagron              | Tretinoin        | 15F01-B06-315491 | 1              |
| Caelo               | Tretinoin        | 15F01-B06-308856 | 1              |
| Euro OTC            | Tretinoin        | 16004059-02      | 1              |
| Caelo               | Tretinoin        | 16070001         | 1              |
| Caelo               | Tretinoin        | 16070002         | 3              |
| Euro OTC            | Tretinoin        | 1612010-01       | 2              |
| Caelo               | Tretinoin        | 16291502         | 2              |
| Caelo               | Tretinoin        | 1612010-01       | 3              |
| Caelo               | Tretinoin        | 16291503         | 3              |

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| Supplier                   | Substance | Batch            | Spectra |
|----------------------------|-----------|------------------|---------|
| Euro OTC                   | Tretinoin | 165070002        | 1       |
| Fagron                     | Tretinoin | 16F14-B04        | 1       |
| gehe                       | Tretinoin | 11225511         | 1       |
| Noweda                     | Tretinoin | 1008021-02       | 1       |
| Euro OTC                   | Tretinoin | 1604059-02       | 3       |
| Caelo                      | Tretinoin | 1517E-02563      | 1       |
| Euro OTC                   | Tretinoin | 161210-01        | 1       |
| Gehe                       | Tretinoin | 1612010-01       | 1       |
| Caelo                      | Tretinoin | 16217108         | 1       |
| Fagron                     | Tretinoin | 16F14B-04        | 1       |
| Fagron                     | Tretinoin | 16F14-B04-326181 | 1       |
| Fagron                     | Tretinoin | 16F14B04325560   | 1       |
| Caelo                      | Tretinoin | 17106101         | 1       |
| Caelo                      | Tretinoin | 3041302          | 1       |
| Euro OTC                   | Tretinoin | 10429AX21        | 1       |
| Caelo                      | Tretinoin | 711212563        | 1       |
| Euro OTC                   | Tretinoin | 1109014-02       | 3       |
| Euro OTC                   | Tretinoin | 1008021-02       | 1       |
| Caelo                      | Tretinoin | 1109014-02       | 1       |
| FARGON                     | Tretinoin | 11a27-n01        | 1       |
| Phoenix am 19.06.2012      | Tretinoin | 11K01-N02        | 1       |
| Fagron                     | Tretinoin | 11K29-N01        | 1       |
| Phönix 08.03.13            | Tretinoin | 11K29-N01        | 1       |
| Sanacorp                   | Tretinoin | 12/06-N01        | 1       |
| Caelo                      | Tretinoin | 12023302         | 12      |
| Caesar & Loretz GmbH, 4... | Tretinoin | 12023302         | 1       |
| Noweda                     | Tretinoin | 12023302         | 2       |
| Caelo                      | Tretinoin | 12102902         | 1       |
| Caelo                      | Tretinoin | 12023309         | 1       |
| Caelo                      | Tretinoin | 12102903         | 4       |
| Caelo                      | Tretinoin | 12320207         | 2       |
| Caelo                      | Tretinoin | 12320205         | 5       |
| Caelo                      | Tretinoin | 12320303         | 1       |
| Caelo                      | Tretinoin | 12367101         | 2       |
| Caelo                      | Tretinoin | 12367103         | 3       |
| Caelo                      | Tretinoin | 12367104         | 1       |
| Fagron                     | Tretinoin | 12D05-N08        | 2       |
| Caelo                      | Tretinoin | 12D05-N08        | 1       |
| Caelo                      | Tretinoin | 12I06-N01        | 1       |
| Fagron                     | Tretinoin | 12I06-N01        | 3       |
| Großhandel                 | Tretinoin | 12I06-N01        | 1       |
| Fagron                     | Tretinoin | 12I06-N01        | 1       |
| Euro OTC                   | Tretinoin | 130102802        | 1       |
| Euro OTC                   | Tretinoin | 1304028-01       | 7       |
| BASF/Phönix                | Tretinoin | 1304028-02       | 2       |
| Caelo                      | Tretinoin | 1304028-02       | 3       |
| Euro OTC                   | Tretinoin | 13041028-01      | 1       |
| Caelo                      | Tretinoin | 13195002         | 16      |
| cealo                      | Tretinoin | 13195002         | 1       |
| Euro OTC                   | Tretinoin | 130402802        | 1       |
| Caelo                      | Tretinoin | 13278101         | 1       |
| Caelo                      | Tretinoin | 13278104         | 3       |
| Caelo                      | Tretinoin | 13278105         | 3       |
| Caelo                      | Tretinoin | 13308003         | 1       |
| Noweda                     | Tretinoin | 13D30-N14        | 1       |
| Caelo                      | Tretinoin | 14093504         | 1       |
| Fagron                     | Tretinoin | 1410001594       | 1       |
| Euro OTC                   | Tretinoin | 14110116-02      | 1       |
| Fagron                     | Tretinoin | 1440104          | 1       |
| Caelo                      | Tretinoin | 20120601         | 1       |

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| Supplier             | Substance | Batch                | Spectra |
|----------------------|-----------|----------------------|---------|
| Fagron               | Tretinoin | 20120601             | 1       |
| Caelo                | Tretinoin | 412051/4             | 1       |
| Caelo                | Tretinoin | 5012I-02563          | 1       |
| Caelo                | Tretinoin | 16F14-B04            | 1       |
| Phönix               | Tretinoin | 1109014-02           | 1       |
| Caelo                | Tretinoin | 12320203             | 3       |
| Caelo                | Tretinoin | 11225511             | 1       |
| Caelo                | Tretinoin | 11k29-n01            | 1       |
| Phoenix              | Tretinoin | 12367103             | 1       |
| Fagron               | Tretinoin | 13D30-N14-3365319091 | 1       |
| Caelo                | Tretinoin | 11225506             | 2       |
| Kehr                 | Tretinoin | 1109014-01           | 1       |
| Caelo                | Tretinoin | 13195008             | 2       |
| Fagron               | Tretinoin | 14009-804            | 1       |
| Phoenix              | Tretinoin | 15F01-B06-317884     | 1       |
| Euro OTC             | Tretinoin | 30042014A            | 1       |
| Caesar & Loretz GmbH | Tretinoin | 11225515             | 1       |
| Caelo                | Tretinoin | 11225504             | 1       |
| Caelo                | Tretinoin | 11284703             | 1       |
| Caelo                | Tretinoin | 12023303             | 1       |
| Caelo                | Tretinoin | 12102904             | 2       |
| Caelo                | Tretinoin | 12320201             | 2       |
| Caelo                | Tretinoin | 12320204             | 1       |
| Caelo                | Tretinoin | 12320209             | 6       |
| Caesar & Loretz GmbH | Tretinoin | 12320211             | 1       |
| Kehr                 | Tretinoin | 12320301             | 1       |
| Sanacorp             | Tretinoin | 12320302             | 1       |
| Caelo                | Tretinoin | 131950002            | 1       |
| Caelo                | Tretinoin | 12320301             | 1       |
| Sanacorp             | Tretinoin | 13195002             | 1       |
| Caelo                | Tretinoin | 395002               | 1       |

- 69 281 spectra from 414 *Apo-Ident* customers from a total of 23 669 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tretinoin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tretinoin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 420           | 0              | 70 966        |
| <b>Type B</b> | 0              | 700           | 1              | 146 028       |
| <b>Type C</b> | 0              | 266           | 86             | 69 281        |

The substance/substance group *Tretinoin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | <b>Specificity</b>       | <b>Recognition rate</b>  |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.5714 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 99.8573 % (> 99.4294 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 75.5682 % (> 74.7159 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 21747            | 21747                      | 0.00                                | 47.39                                  |
| 21757            | 21757                      | 0.00                                | 47.98                                  |
| 21878            | 21747                      | 10.43                               | 49.66                                  |
| 21940            | 21940                      | 0.00                                | 47.17                                  |
| 22574            | 22574                      | 0.00                                | 47.18                                  |
| 22936            | 21940                      | 2.43                                | 46.83                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Triamcinolon, micronized**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20564-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Triamcinolon, micronized; Triamcinolonum micronisatum

### Special notes

When selecting the *Triamcinolon, micronized* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Triamcinolon, micronized*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Fagron   | Triamcinolon, mi... | 12A03-N09        | 20730     | 40      | 20120117           |
| Fagron   | Triamcinolon, mi... | 12K07-N13        | 20936     | 80      | AR-15-FG-003373-01 |
| Caelo    | Triamcinolon, mi... | 15106905         | 22273     | 30      | 20150527           |
| Fagron   | Triamcinolon, mi... | 14B13-B30-316101 | 22840     | 40      | 20140311           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 190 spectra of 4 reference samples from the substance/substance group *Triamcinolon, micronized*. These samples are listed above in the [calibration samples](#) section.
- 71 196 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 125 spectra of 4 reference samples from the substance/substance group *Triamcinolon, micronized*.

| Supplier | Substance                | Batch     | Sample ID          | Spectra |
|----------|--------------------------|-----------|--------------------|---------|
| Fagron   | Triamcinolon, micronized | 12A03-N09 | 20564              | 40      |
| Caelo    | Triamcinolon, micronized | 15106905  | 22273 <sup>†</sup> | 15      |
| Caelo    | Triamcinolon, micronized | 15106905  | 22605              | 40      |
| Caelo    | Triamcinolon, micronized | 15106911  | 23508              | 30      |

- 146 604 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 30 spectra from 21 *Apo-Ident* customers from 21 batches from the substance/substance group *Triamcinolon, micronized*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



| Supplier          | Substance                | Batch            | Spectra |
|-------------------|--------------------------|------------------|---------|
| Sanacorp          | Triamcinolon, micronized | 100/AKD6         | 1       |
| Caelo             | Triamcinolon, micronized | 12295207         | 1       |
| Caelo             | Triamcinolon, micronized | 12295210         | 2       |
| Fagron            | Triamcinolon, micronized | 12D02-N14        | 1       |
| Fagron            | Triamcinolon, micronized | 12F01-N19        | 4       |
| Fagron            | Triamcinolon, micronized | 12K07-N13        | 1       |
| Fagron            | Triamcinolon, micronized | 13D30-N15        | 2       |
| Fagron            | Triamcinolon, micronized | 13C26-N04        | 2       |
| Caelo             | Triamcinolon, micronized | 13J07-N08        | 2       |
| Noweda 24.08.2015 | Triamcinolon, micronized | 14B13-B30-293474 | 1       |
| Fagron            | Triamcinolon, micronized | 14B13-B30-293474 | 1       |
| Fagron            | Triamcinolon, micronized | 14B13-B30-312868 | 1       |
| Caelo             | Triamcinolon, micronized | 15106902         | 1       |
| Caelo             | Triamcinolon, micronized | 15106960         | 1       |
| Fagron            | Triamcinolon, micronized | 15B13-B30-312868 | 1       |
| Caelo             | Triamcinolon, micronized | AKD15            | 1       |
| Phönix            | Triamcinolon, micronized | NS0608M          | 1       |
| Fagron            | Triamcinolon, micronized | 11D28-N04        | 1       |
| Fagron            | Triamcinolon, micronized | 11G26-N04        | 1       |
| Caelo             | Triamcinolon, micronized | 12146612         | 1       |
| Fagron            | Triamcinolon, micronized | 12Do2-N14        | 1       |
| Fagron            | Triamcinolon, micronized | 12A03-N09        | 2       |

- 69 603 spectra from 414 *Apo-Ident* customers from a total of 23 782 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Triamcinolon, micronized* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Triamcinolon, micronized* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 190           | 0              | 71 196        |
| <b>Type B</b> | 0              | 85            | 40             | 146 604       |
| <b>Type C</b> | 0              | 25            | 5              | 69 603        |

The substance/substance group *Triamcinolon, micronized* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.8421 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 68.0000 % (> 65.6000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 83.3333 % (> 73.3333 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20730     | 20936               | 19.58                        | 46.29                           |
| 20936     | 20936               | 0.00                         | 51.05                           |
| 22273     | 20936               | 3.32                         | 50.84                           |
| 22840     | 20936               | 11.31                        | 46.91                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Triamcinolone acetonide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20765-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Triamcinolone acetonide; Triamcinoloni acetonidum; Triamcinolonum acetonatum

### Special notes

When selecting the *Triamcinolone acetonide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Triamcinolone acetonide*:

| Supplier | Substance           | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------|-----------|---------|--------------------|
| Fagron   | Triamcinolone ac... | 12E15-N03  | 20765     | 40      | 1412051            |
| Euro OTC | Triamcinolone ac... | 1303001-02 | 20910     | 40      | 20130815           |
| Caelo    | Triamcinolone ac... | 13256607   | 21061     | 80      | AR-15-FG-003755-01 |
| Euro OTC | Triamcinolone ac... | 1211013-02 | 21072     | 30      | 20130417           |
| Caelo    | Triamcinolone ac... | 13379921   | 21587     | 40      | 1503634            |

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| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Euro OTC | Triamcinolone ac... | 1508008          | 21883     | 40      | 20150902*   |
| Fagron   | Triamcinolone ac... | 15C19-B06-308572 | 21962     | 40      | 20150402    |
| Euro OTC | Triamcinolone ac... | 1601021          | 22313     | 30      | 20160119*   |
| Euro OTC | Triamcinolone ac... | 1605010          | 22572     | 40      | 20160531*   |
| Euro OTC | Triamcinolone ac... | 1608005          | 22752     | 40      | 20160906*   |
| Euro OTC | Triamcinolone ac... | 1605010          | 22572SI   | 25      | 20160531*   |
| Euro OTC | Triamcinolone ac... | 1608005          | 22752SI   | 22      | 20160906*   |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 467 spectra of 12 reference samples from the substance/substance group *Triamcinolone acetone*. These samples are listed above in the [calibration samples](#) section.
- 70919 spectra from a total of 1542 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 711 spectra of 24 reference samples from the substance/substance group *Triamcinolone acetone*.

| Supplier | Substance             | Batch            | Sample ID          | Spectra |
|----------|-----------------------|------------------|--------------------|---------|
| Caelo    | Triamcinolone acetone | 80890079         | 20007              | 20      |
| Fagron   | Triamcinolone acetone | 12E15-N03        | 20765 <sup>†</sup> | 10      |
| Caelo    | Triamcinolone acetone | 12301505         | 20769              | 50      |
| Fagron   | Triamcinolone acetone | 13C13-N20        | 21043              | 40      |
| Caelo    | Triamcinolone acetone | 13379921         | 21587 <sup>†</sup> | 20      |
| Euro OTC | Triamcinolone acetone | 1508008          | 21883 <sup>†</sup> | 20      |
| Fagron   | Triamcinolone acetone | 15C19-B06-308572 | 21962 <sup>†</sup> | 20      |
| Euro OTC | Triamcinolone acetone | 1601021          | 22313 <sup>†</sup> | 15      |
| Caelo    | Triamcinolone acetone | 160945           | 22473              | 60      |
| Euro OTC | Triamcinolone acetone | 1612014          | 22978              | 40      |
| Caelo    | Triamcinolone acetone | 171206           | 23330              | 40      |
| Caelo    | Triamcinolone acetone | 171206           | 23343              | 40      |

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\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

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| Supplier | Substance               | Batch            | Sample ID | Spectra |
|----------|-------------------------|------------------|-----------|---------|
| Euro OTC | Triamcinolone acetonide | 1703037          | 23393     | 38      |
| Euro OTC | Triamcinolone acetonide | 1706013          | 23557     | 40      |
| Euro OTC | Triamcinolone acetonide | 1710002          | 23694     | 40      |
| Euro OTC | Triamcinolone acetonide | 1508008          | 21883SI   | 30      |
| Fagron   | Triamcinolone acetonide | 15C19-B06-308572 | 21962SI   | 19      |
| Caelo    | Triamcinolone acetonide | 160945           | 22473SI   | 40      |
| Euro OTC | Triamcinolone acetonide | 1612014          | 22978SI   | 29      |
| Caelo    | Triamcinolone acetonide | 171206           | 23330SI   | 20      |
| Caelo    | Triamcinolone acetonide | 171206           | 23343SI   | 20      |
| Euro OTC | Triamcinolone acetonide | 1703037          | 23393SI   | 20      |
| Euro OTC | Triamcinolone acetonide | 1706013          | 23557SI   | 20      |
| Euro OTC | Triamcinolone acetonide | 1710002          | 23694SI   | 20      |

- 146 018 spectra from a total of 3180 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1333 spectra from 310 *Apo-Ident* customers from 336 batches from the substance/substance group *Triamcinolone acetonide*.

| Supplier     | Substance               | Batch      | Spectra |
|--------------|-------------------------|------------|---------|
| Caelo        | Triamcinolone acetonide | 13124805   | 10      |
| Euro OTC     | Triamcinolone acetonide | 3022015A   | 1       |
| Euro OTC     | Triamcinolone acetonide | 3051402    | 1       |
| Fagron       | Triamcinolone acetonide | 4111408    | 1       |
| Fagron       | Triamcinolone acetonide | 7041501    | 1       |
| Caelo        | Triamcinolone acetonide | 6051401    | 1       |
| Caelo        | Triamcinolone acetonide | 100/AKD2   | 1       |
| Euro OTC     | Triamcinolone acetonide | 1008005-01 | 1       |
| Sanacorp     | Triamcinolone acetonide | 100/AKD4   | 1       |
| Caelo        | Triamcinolone acetonide | 102/AKD12  | 1       |
| Caelo        | Triamcinolone acetonide | 102/AKD11  | 1       |
| Caelo        | Triamcinolone acetonide | 12031601   | 1       |
| Fagron       | Triamcinolone acetonide | 11K11-N10  | 6       |
| Fagron       | Triamcinolone acetonide | 12/-N09    | 1       |
| Caelo        | Triamcinolone acetonide | 1206008-01 | 1       |
| Euro OTC     | Triamcinolone acetonide | 1211013-01 | 9       |
| Caelo        | Triamcinolone acetonide | 12173703   | 1       |
| Euro OTC     | Triamcinolone acetonide | 1211013-02 | 13      |
| Caelo        | Triamcinolone acetonide | 12301502   | 1       |
| Caelo        | Triamcinolone acetonide | 12301505   | 1       |
| Fargon/Anzag | Triamcinolone acetonide | 13/26-N11  | 3       |
| Fagron       | Triamcinolone acetonide | 13/26-N11  | 6       |
| Fagron       | Triamcinolone acetonide | 1326-N11   | 1       |

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<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

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| Supplier                   | Substance               | Batch            | Spectra |
|----------------------------|-------------------------|------------------|---------|
| Fagron                     | Triamcinolone acetonide | 13/26-N11        | 1       |
| Euro OTC                   | Triamcinolone acetonide | 1307043-02       | 12      |
| Caelo                      | Triamcinolone acetonide | 1307043-01       | 2       |
| Euro OTC                   | Triamcinolone acetonide | 1303001-02       | 8       |
| Euro OTC                   | Triamcinolone acetonide | 1307043-01       | 12      |
| EuRho/Phönix               | Triamcinolone acetonide | 1307043-02       | 1       |
| Caelo                      | Triamcinolone acetonide | 13124801         | 6       |
| Caelo                      | Triamcinolone acetonide | 13124804         | 15      |
| Caelo                      | Triamcinolone acetonide | 13124807         | 9       |
| Caelo                      | Triamcinolone acetonide | 13124808         | 15      |
| Gepepharm/Noweda           | Triamcinolone acetonide | 13124808         | 1       |
| Caelo                      | Triamcinolone acetonide | 13124810         | 4       |
| Caelo                      | Triamcinolone acetonide | 13124811         | 2       |
| Caelo                      | Triamcinolone acetonide | 13124809         | 2       |
| Caelo                      | Triamcinolone acetonide | 13256603         | 1       |
| Caelo                      | Triamcinolone acetonide | 13256604         | 7       |
| Caelo                      | Triamcinolone acetonide | 13256606         | 1       |
| Sanacorp                   | Triamcinolone acetonide | 1326N11          | 1       |
| Caelo                      | Triamcinolone acetonide | 13256608         | 2       |
| Caelo                      | Triamcinolone acetonide | 13379901         | 1       |
| Caelo                      | Triamcinolone acetonide | 13256607         | 4       |
| Phönix                     | Triamcinolone acetonide | 13379902         | 1       |
| Caelo                      | Triamcinolone acetonide | 13379902         | 1       |
| Caelo                      | Triamcinolone acetonide | 13379904         | 6       |
| Caelo                      | Triamcinolone acetonide | 13379903         | 2       |
| VDL                        | Triamcinolone acetonide | 13379903         | 1       |
| Caelo                      | Triamcinolone acetonide | 13379905         | 15      |
| Martinus-Apotheke          | Triamcinolone acetonide | 13379905         | 1       |
| Sanacorp                   | Triamcinolone acetonide | 13379905         | 1       |
| Caesar & Loretz GmbH Hi... | Triamcinolone acetonide | 13379905         | 1       |
| Caelo                      | Triamcinolone acetonide | 13379906         | 8       |
| Caelo                      | Triamcinolone acetonide | 13379912         | 9       |
| Caelo                      | Triamcinolone acetonide | 13379911         | 2       |
| Euro OTC                   | Triamcinolone acetonide | 13379912         | 2       |
| Caelo                      | Triamcinolone acetonide | 13379913         | 4       |
| Caelo                      | Triamcinolone acetonide | 13379914         | 7       |
| Caelo                      | Triamcinolone acetonide | 13379922         | 1       |
| Caelo                      | Triamcinolone acetonide | 13379921         | 1       |
| Caelo                      | Triamcinolone acetonide | 13379919         | 1       |
| Fagron                     | Triamcinolone acetonide | 13C13-N20        | 16      |
| Caelo                      | Triamcinolone acetonide | 1355101          | 1       |
| Fagron                     | Triamcinolone acetonide | 13c13-n20        | 2       |
| Fagron                     | Triamcinolone acetonide | 13E15-N03        | 50      |
| Fagron                     | Triamcinolone acetonide | 13E15N03         | 3       |
| Phönix                     | Triamcinolone acetonide | 13E15-N03        | 1       |
| Fagron                     | Triamcinolone acetonide | 13E15-N03        | 1       |
| Fagron                     | Triamcinolone acetonide | 13I26-N11        | 16      |
| Caelo                      | Triamcinolone acetonide | 13I26-N11        | 1       |
| Fagron                     | Triamcinolone acetonide | 13I26N11         | 1       |
| Fagron                     | Triamcinolone acetonide | 13I26-N26        | 1       |
| Fagron                     | Triamcinolone acetonide | 13K14-B04        | 4       |
| Fagron                     | Triamcinolone acetonide | 13K14-b04        | 1       |
| Fagron                     | Triamcinolone acetonide | 13K14-B04-289032 | 3       |
| Fagron                     | Triamcinolone acetonide | 13K14-B04-289033 | 9       |
| Caelo                      | Triamcinolone acetonide | 13K14-B04-289033 | 2       |
| Fagron                     | Triamcinolone acetonide | 13K15-B31        | 8       |
| Fagron                     | Triamcinolone acetonide | 13K15-B31-289031 | 6       |
| Bombastus                  | Triamcinolone acetonide | 13K15-B31        | 2       |
| Fagron                     | Triamcinolone acetonide | 13K15-B31-289027 | 6       |
| Caelo                      | Triamcinolone acetonide | 13K15-B31-289027 | 2       |

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| Supplier          | Substance             | Batch            | Spectra |
|-------------------|-----------------------|------------------|---------|
| Fagron            | Triamcinolone acetone | 13K15-B31-289025 | 1       |
| Phönix            | Triamcinolone acetone | 13K15-B31-289027 | 1       |
| Fagron            | Triamcinolone acetone | 13K15B31289029   | 1       |
| Noweda            | Triamcinolone acetone | 13K15-B31-289029 | 1       |
| Fagron            | Triamcinolone acetone | 13K15-B31-289029 | 4       |
| Fagron            | Triamcinolone acetone | 13k15-b31-289029 | 2       |
| Caelo             | Triamcinolone acetone | 13K15-B31-289029 | 1       |
| Fargon            | Triamcinolone acetone | 13K15-B31-289030 | 1       |
| Fagron            | Triamcinolone acetone | 13k15-b31-289030 | 1       |
| Fagron            | Triamcinolone acetone | 13K15B31289031   | 1       |
| Phoenix           | Triamcinolone acetone | 13126-N11        | 2       |
| Caelo             | Triamcinolone acetone | 13K15-B31-289031 | 1       |
| Euro OTC          | Triamcinolone acetone | 14030009-02      | 1       |
| Euro OTC          | Triamcinolone acetone | 14030009-01      | 2       |
| euroct/gehe       | Triamcinolone acetone | 1403009          | 1       |
| Euro OTC          | Triamcinolone acetone | 1403009-01       | 8       |
| Phönix            | Triamcinolone acetone | 1403009-01       | 1       |
| Euro OTC          | Triamcinolone acetone | 1403009-02       | 13      |
| euroct/gehe       | Triamcinolone acetone | 1403009-02       | 1       |
| EuRho             | Triamcinolone acetone | 1403009-02       | 1       |
| EuRho/Phoenix     | Triamcinolone acetone | 1403009-02       | 1       |
| Euro OTC          | Triamcinolone acetone | 1407044-01       | 9       |
| Newchem/Kehr      | Triamcinolone acetone | 1407044-01       | 1       |
| EuRho/Phönix      | Triamcinolone acetone | 1407044-01       | 1       |
| Phönix            | Triamcinolone acetone | 1407044-01       | 1       |
| Bombastus         | Triamcinolone acetone | 140704401        | 1       |
| Fagron            | Triamcinolone acetone | 1407044-01       | 1       |
| Euro OTC          | Triamcinolone acetone | 1407044-02       | 17      |
| Euro OTC          | Triamcinolone acetone | 14120130         | 1       |
| Euro OTC          | Triamcinolone acetone | 1412013-01       | 14      |
| Euro OTC          | Triamcinolone acetone | 141201301        | 1       |
| Euro OTC          | Triamcinolone acetone | 1412013-02       | 7       |
| Euro OTC          | Triamcinolone acetone | 141201302        | 2       |
| Euro OTC          | Triamcinolone acetone | 141213-02        | 1       |
| Caelo             | Triamcinolone acetone | 14188301         | 1       |
| Caelo             | Triamcinolone acetone | 14188302         | 1       |
| Caelo             | Triamcinolone acetone | 14188303         | 4       |
| Euro OTC          | Triamcinolone acetone | 14188304         | 1       |
| Caelo             | Triamcinolone acetone | 14188304         | 3       |
| Caelo             | Triamcinolone acetone | 14355101         | 14      |
| Caelo             | Triamcinolone acetone | 14255104         | 1       |
| Caelo             | Triamcinolone acetone | 14233904         | 1       |
| Berkel AHK        | Triamcinolone acetone | 14355101         | 3       |
| AHD 06.03.15 9,47 | Triamcinolone acetone | 14355102         | 2       |
| Caelo             | Triamcinolone acetone | 14355102         | 12      |
| Caelo             | Triamcinolone acetone | 14355103         | 9       |
| Noweda            | Triamcinolone acetone | 14355103         | 1       |
| Caelo             | Triamcinolone acetone | 14355104         | 4       |
| Fagron            | Triamcinolone acetone | 14355104         | 1       |
| Caelo             | Triamcinolone acetone | 14355702         | 13      |
| Caelo             | Triamcinolone acetone | 14355703         | 3       |
| Caelo             | Triamcinolone acetone | 14355704         | 2       |
| Caelo             | Triamcinolone acetone | 14355708         | 8       |
| Caelo             | Triamcinolone acetone | 14355706         | 1       |
| Noweda            | Triamcinolone acetone | 14355708         | 1       |
| Fagron            | Triamcinolone acetone | 14355709         | 1       |
| Caelo             | Triamcinolone acetone | 14355709         | 1       |
| Phoenix           | Triamcinolone acetone | 14355709         | 1       |
| Caelo             | Triamcinolone acetone | 14355711         | 9       |
| Phönix Gotha      | Triamcinolone acetone | 14355711         | 1       |

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| Supplier                   | Substance               | Batch            | Spectra |
|----------------------------|-------------------------|------------------|---------|
| AHD                        | Triamcinolone acetonide | 14355711         | 1       |
| Caelo                      | Triamcinolone acetonide | 14355712         | 2       |
| Fagron                     | Triamcinolone acetonide | 14F30-B01        | 2       |
| Fagron                     | Triamcinolone acetonide | 14F30B01         | 1       |
| Fagron                     | Triamcinolone acetonide | 14F30-B01-296287 | 1       |
| Caelo                      | Triamcinolone acetonide | 14G23B072976618  | 1       |
| Fagron                     | Triamcinolone acetonide | 14G23-B07        | 1       |
| Fagron                     | Triamcinolone acetonide | 14G23-B07-297618 | 3       |
| Fagron                     | Triamcinolone acetonide | 14G23-B07-297619 | 2       |
| Fagron                     | Triamcinolone acetonide | 14G23-B07-297620 | 5       |
| Fagron                     | Triamcinolone acetonide | 14k14-B05-302887 | 1       |
| Fagron                     | Triamcinolone acetonide | 14K14-B05-302887 | 1       |
| NEWCHEM / Sanacorp         | Triamcinolone acetonide | 15040007-01      | 1       |
| Euro OTC                   | Triamcinolone acetonide | 1504007-01       | 12      |
| Caelo                      | Triamcinolone acetonide | 1504007-01       | 1       |
| Euro OTC                   | Triamcinolone acetonide | 1504007-02       | 12      |
| Euro OTC                   | Triamcinolone acetonide | 15042014A        | 1       |
| Euro OTC                   | Triamcinolone acetonide | 15041007-02      | 1       |
| Euro OTC                   | Triamcinolone acetonide | 1508008-01       | 11      |
| Caelo                      | Triamcinolone acetonide | 1508008-01       | 1       |
| Euro OTC                   | Triamcinolone acetonide | 1508008-02       | 10      |
| EuRho                      | Triamcinolone acetonide | 1508008-02       | 2       |
| Euro OTC                   | Triamcinolone acetonide | 150800802        | 2       |
| Sittig                     | Triamcinolone acetonide | 1508008-02       | 1       |
| Caelo                      | Triamcinolone acetonide | 1508008-02       | 1       |
| Caelo                      | Triamcinolone acetonide | 15233901         | 11      |
| Caelo                      | Triamcinolone acetonide | 1514Q2516        | 1       |
| Farmabios S.p.A./Caesar... | Triamcinolone acetonide | 15233901         | 1       |
| Caelo                      | Triamcinolone acetonide | 15233902         | 18      |
| Sanacorp                   | Triamcinolone acetonide | 15233902         | 2       |
| AHD/Hedinger               | Triamcinolone acetonide | 15233902         | 1       |
| Noweda                     | Triamcinolone acetonide | 15233902         | 1       |
| Caelo                      | Triamcinolone acetonide | 15233903         | 13      |
| Noweda                     | Triamcinolone acetonide | 15233903         | 1       |
| Euro OTC                   | Triamcinolone acetonide | 15233904         | 1       |
| Caelo                      | Triamcinolone acetonide | 15233904         | 10      |
| Caelo                      | Triamcinolone acetonide | 15233905         | 4       |
| Caelo                      | Triamcinolone acetonide | 15233906         | 10      |
| Euro OTC                   | Triamcinolone acetonide | 15233906         | 1       |
| Caelo                      | Triamcinolone acetonide | 15233908         | 3       |
| Caelo                      | Triamcinolone acetonide | 15430101         | 1       |
| Caelo                      | Triamcinolone acetonide | 15430102         | 3       |
| Audor Pharma               | Triamcinolone acetonide | 15240T           | 1       |
| Euro OTC                   | Triamcinolone acetonide | 15404007-01      | 1       |
| Gehe                       | Triamcinolone acetonide | 15430102         | 1       |
| Caelo                      | Triamcinolone acetonide | 15430103         | 1       |
| Caelo                      | Triamcinolone acetonide | 15430105         | 7       |
| Caelo                      | Triamcinolone acetonide | 15430106         | 4       |
| Caelo                      | Triamcinolone acetonide | 15430107         | 4       |
| Caelo                      | Triamcinolone acetonide | 15430108         | 3       |
| Fagron                     | Triamcinolone acetonide | 15B02-B03        | 4       |
| Newchem S.p.A./Caesar &... | Triamcinolone acetonide | 1543015          | 1       |
| Fagron                     | Triamcinolone acetonide | 15B02-B03-303827 | 2       |
| Fagron                     | Triamcinolone acetonide | 15B02-B03-303828 | 3       |
| Fargon/Alliance HC         | Triamcinolone acetonide | 15B02-B03-303830 | 1       |
| Fagron                     | Triamcinolone acetonide | 15B02-B03-303830 | 7       |
| Fagron                     | Triamcinolone acetonide | 15C19-B06        | 1       |
| Fagron                     | Triamcinolone acetonide | 15B02-B03-303828 | 1       |
| Caelo                      | Triamcinolone acetonide | 15C19-B06-308571 | 1       |
| Fagron                     | Triamcinolone acetonide | 15C19-B06-308571 | 1       |

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| Supplier              | Substance             | Batch            | Spectra |
|-----------------------|-----------------------|------------------|---------|
| Fagron                | Triamcinolone acetone | 15C19-B06-308572 | 4       |
| Caelo                 | Triamcinolone acetone | 15C19-B06-308573 | 1       |
| Fagron                | Triamcinolone acetone | 15C19-B06-308573 | 5       |
| Fagron                | Triamcinolone acetone | 15G31B07         | 1       |
| Fagron                | Triamcinolone acetone | 15G31-B07        | 1       |
| Fagron                | Triamcinolone acetone | 15C19-B06-309194 | 1       |
| Fagron                | Triamcinolone acetone | 15G31-B07-313596 | 4       |
| Fagron                | Triamcinolone acetone | 15G31-B07-313597 | 3       |
| Fagron                | Triamcinolone acetone | 15G31-B07-314045 | 3       |
| Caelo                 | Triamcinolone acetone | 15G31-B07-313597 | 1       |
| Fagron                | Triamcinolone acetone | 15g31-b07-314046 | 1       |
| Caelo                 | Triamcinolone acetone | 15L21-B03-316123 | 1       |
| Fagron                | Triamcinolone acetone | 15L21-B03-316123 | 2       |
| Fagron                | Triamcinolone acetone | 15G31-B07-314047 | 1       |
| Euro OTC              | Triamcinolone acetone | 15L21-B03-316123 | 2       |
| Euro OTC              | Triamcinolone acetone | 1601021-01       | 19      |
| Caelo                 | Triamcinolone acetone | 15L21-B03-318663 | 1       |
| Fagron                | Triamcinolone acetone | 15L21-B03-318663 | 2       |
| EuRho                 | Triamcinolone acetone | 1601021-01       | 1       |
| Caelo                 | Triamcinolone acetone | 160102101        | 1       |
| Euro OTC              | Triamcinolone acetone | 1605010-01       | 20      |
| Caelo                 | Triamcinolone acetone | 1605010-01       | 2       |
| Newchem/Fiebig        | Triamcinolone acetone | 1605010-01       | 1       |
| Euro OTC              | Triamcinolone acetone | 1608005-01       | 11      |
| Euro OTC              | Triamcinolone acetone | 1608005          | 1       |
| Caelo                 | Triamcinolone acetone | 1608005-01       | 1       |
| Caelo                 | Triamcinolone acetone | 16092504         | 7       |
| Calo/Sanacorp         | Triamcinolone acetone | 16092504         | 1       |
| Sanacorp              | Triamcinolone acetone | 16094501         | 1       |
| Caelo                 | Triamcinolone acetone | 16094501         | 8       |
| Gehe                  | Triamcinolone acetone | 16094501         | 1       |
| Caelo                 | Triamcinolone acetone | 16094506         | 1       |
| Caelo                 | Triamcinolone acetone | 16094505         | 1       |
| Caelo                 | Triamcinolone acetone | 16094504         | 1       |
| Caelo                 | Triamcinolone acetone | 16094511         | 4       |
| Caelo                 | Triamcinolone acetone | 16094507         | 1       |
| Caelo                 | Triamcinolone acetone | 16094512         | 3       |
| Caelo                 | Triamcinolone acetone | 16094514         | 3       |
| Euro OTC              | Triamcinolone acetone | 1612014-01       | 20      |
| Euro/Noweda           | Triamcinolone acetone | 161201401        | 1       |
| Ebert/Euo             | Triamcinolone acetone | 1612014-01       | 1       |
| Caelo                 | Triamcinolone acetone | 1612014-01       | 1       |
| Fagron                | Triamcinolone acetone | 16B04-B07        | 1       |
| Fagron                | Triamcinolone acetone | 16B04-B07-318664 | 2       |
| Fagron                | Triamcinolone acetone | 16B04-B07-318957 | 3       |
| Caelo                 | Triamcinolone acetone | 16D14-B11        | 1       |
| Fagron                | Triamcinolone acetone | 16D14-B11-322136 | 2       |
| Fagron                | Triamcinolone acetone | 16D14-B11-322135 | 1       |
| AHD 22.12.16 EK 29,74 | Triamcinolone acetone | 16D14B11322136   | 1       |
| Fagron                | Triamcinolone acetone | 16D14-B11-322158 | 1       |
| Fagron                | Triamcinolone acetone | 16D14-B11-325479 | 2       |
| Fagron                | Triamcinolone acetone | 16D14-B11-325480 | 3       |
| Fagron                | Triamcinolone acetone | 16D14-B11-325481 | 1       |
| Fagron                | Triamcinolone acetone | 16D14-B11-325482 | 1       |
| Fagron                | Triamcinolone acetone | 16K07-B06        | 1       |
| Fagron                | Triamcinolone acetone | 16K07-B06-329445 | 1       |
| Fagron                | Triamcinolone acetone | 16F07-B06        | 1       |
| Caelo                 | Triamcinolone acetone | 170303701        | 1       |
| Caelo                 | Triamcinolone acetone | 17057901         | 1       |
| Euro OTC              | Triamcinolone acetone | 1703037-01       | 1       |

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| Supplier                   | Substance               | Batch           | Spectra |
|----------------------------|-------------------------|-----------------|---------|
| Caelo                      | Triamcinolone acetonide | 17057902        | 2       |
| Caelo                      | Triamcinolone acetonide | 17057906        | 2       |
| Euro OTC                   | Triamcinolone acetonide | 26081405        | 1       |
| Euro OTC                   | Triamcinolone acetonide | 17061406        | 1       |
| Euro OTC                   | Triamcinolone acetonide | 29011503        | 1       |
| Euro OTC                   | Triamcinolone acetonide | 29081501        | 1       |
| Euro OTC                   | Triamcinolone acetonide | 31101414        | 1       |
| Fagron                     | Triamcinolone acetonide | 289027          | 1       |
| euro/ Anzag                | Triamcinolone acetonide | 3315I02516      | 1       |
| Caelo                      | Triamcinolone acetonide | 5430105         | 1       |
| Fagron                     | Triamcinolone acetonide | 700124-0004     | 1       |
| AUDOER/ Alliance Health... | Triamcinolone acetonide | APB0544/112020T | 1       |
| Audor Pharma               | Triamcinolone acetonide | APB0544/112020T | 1       |
| Euro OTC                   | Triamcinolone acetonide | APB0544/112020T | 1       |
| Audor Pharma               | Triamcinolone acetonide | APU0544/31524T  | 1       |
| Audor Pharma               | Triamcinolone acetonide | APU0544/315240T | 2       |
| Oberlinden Apotheke        | Triamcinolone acetonide | B0544/114010    | 1       |
| Fagron                     | Triamcinolone acetonide | NT077oM         | 1       |
| Anzag                      | Triamcinolone acetonide | APB0544/112020T | 1       |
| Fagron                     | Triamcinolone acetonide | NT1430M         | 2       |
| Fagron                     | Triamcinolone acetonide | NT1094M         | 1       |
| AHD 03.03.2015             | Triamcinolone acetonide | NT1430M         | 1       |
| NEWCHEM S.P.A.             | Triamcinolone acetonide | NV0994M         | 1       |
| Fagron                     | Triamcinolone acetonide | NU0930M         | 1       |
| Fagron                     | Triamcinolone acetonide | NV0262M         | 2       |
| Oberlinden-Apotheke        | Triamcinolone acetonide | U0544/1         | 1       |
| Fagron                     | Triamcinolone acetonide | Nw0635M         | 1       |
| Eigen/Defektur             | Triamcinolone acetonide | U0544/113530    | 1       |
| Audor Pharma               | Triamcinolone acetonide | U0544/315240T   | 1       |
| Caelo                      | Triamcinolone acetonide | 1811211         | 1       |
| Fagron                     | Triamcinolone acetonide | 5061303         | 1       |
| Fagron                     | Triamcinolone acetonide | 5121302         | 1       |
| Fagron                     | Triamcinolone acetonide | 5061205         | 1       |
| Caelo                      | Triamcinolone acetonide | 3041206         | 1       |
| Euro OTC                   | Triamcinolone acetonide | 80616-5         | 1       |
| Fagron                     | Triamcinolone acetonide | 7H30-N03        | 1       |
| Caelo                      | Triamcinolone acetonide | 9081305         | 1       |
| Fagron                     | Triamcinolone acetonide | 9041305         | 1       |
| Euro OTC                   | Triamcinolone acetonide | 1013I-02516     | 1       |
| Caelo                      | Triamcinolone acetonide | 9364429         | 2       |
| Caelo                      | Triamcinolone acetonide | 10220311        | 1       |
| Caelo                      | Triamcinolone acetonide | 10220332        | 1       |
| Caelo                      | Triamcinolone acetonide | 10220340        | 2       |
| Caelo                      | Triamcinolone acetonide | 10220341        | 1       |
| Caelo                      | Triamcinolone acetonide | 1107212516      | 1       |
| Caelo                      | Triamcinolone acetonide | 10220342        | 1       |
| Anzag, 24.10.2012          | Triamcinolone acetonide | 1110004-01      | 1       |
| Euro OTC                   | Triamcinolone acetonide | 1110005-01      | 4       |
| Euro OTC                   | Triamcinolone acetonide | 1110004-01      | 1       |
| Euro OTC                   | Triamcinolone acetonide | 111005-01       | 1       |
| Caelo                      | Triamcinolone acetonide | 1110005-01      | 1       |
| Fagron                     | Triamcinolone acetonide | 11101208        | 1       |
| Euro OTC                   | Triamcinolone acetonide | 1112023-01      | 3       |
| Euro OTC                   | Triamcinolone acetonide | 1112023-02      | 10      |
| Noweda                     | Triamcinolone acetonide | 1112023-02      | 1       |
| Caelo                      | Triamcinolone acetonide | 11267706        | 1       |
| Caesar&loretz,Phoenix      | Triamcinolone acetonide | 11267705        | 1       |
| Caelo                      | Triamcinolone acetonide | 11267705        | 1       |
| Caelo                      | Triamcinolone acetonide | 11267707        | 4       |
| Caelo                      | Triamcinolone acetonide | 11267704        | 1       |

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| Supplier                  | Substance               | Batch      | Spectra |
|---------------------------|-------------------------|------------|---------|
| Caelo                     | Triamcinolone acetonide | 11267710   | 2       |
| Phönix Gotha              | Triamcinolone acetonide | 11267711   | 1       |
| Caelo                     | Triamcinolone acetonide | 11267711   | 1       |
| Caelo                     | Triamcinolone acetonide | 11267721   | 4       |
| Caelo                     | Triamcinolone acetonide | 11267714   | 1       |
| Gehe                      | Triamcinolone acetonide | 11267721   | 1       |
| Caelo                     | Triamcinolone acetonide | 11267720   | 1       |
| anzag am 29.06.2012       | Triamcinolone acetonide | 11267720   | 1       |
| Caelo                     | Triamcinolone acetonide | 11K11-N10  | 1       |
| Fagron                    | Triamcinolone acetonide | 11B22-N05  | 1       |
| Fagron                    | Triamcinolone acetonide | 12/10-N09  | 5       |
| Gehe                      | Triamcinolone acetonide | 12/10-N09  | 2       |
| Caelo                     | Triamcinolone acetonide | 12/10-N09  | 3       |
| Caelo                     | Triamcinolone acetonide | 1201506    | 1       |
| Euro OTC                  | Triamcinolone acetonide | 1206008-01 | 5       |
| Europharm/Otto            | Triamcinolone acetonide | 1206008-01 | 1       |
| Euro OTC                  | Triamcinolone acetonide | 1209040-01 | 4       |
| Fagron                    | Triamcinolone acetonide | 120600801  | 1       |
| Caelo                     | Triamcinolone acetonide | 1209040-01 | 1       |
| Gehe/Phönix               | Triamcinolone acetonide | 1209040-02 | 1       |
| Euro OTC                  | Triamcinolone acetonide | 1209040-02 | 4       |
| Europharm/Otto            | Triamcinolone acetonide | 1209040-02 | 1       |
| Caelo                     | Triamcinolone acetonide | 120904002  | 1       |
| Caelo                     | Triamcinolone acetonide | 1210-n09   | 1       |
| Europharm/Sanacorp        | Triamcinolone acetonide | 1211013-01 | 3       |
| Caelo                     | Triamcinolone acetonide | 1211013-01 | 1       |
| Gehe                      | Triamcinolone acetonide | 1211013-01 | 2       |
| EuRho/Phönix              | Triamcinolone acetonide | 1211013-01 | 1       |
| Noweda/ NEWCHEM           | Triamcinolone acetonide | 1211013-02 | 1       |
| GEHE                      | Triamcinolone acetonide | 1211013-02 | 1       |
| A.H. 07.05.13 ek: 7,25EUR | Triamcinolone acetonide | 1211013-02 | 1       |
| Euro OTC                  | Triamcinolone acetonide | 121113-02  | 1       |
| euro                      | Triamcinolone acetonide | 1211013-02 | 1       |
| Caelo                     | Triamcinolone acetonide | 1217307    | 1       |
| Caelo                     | Triamcinolone acetonide | 12173701   | 8       |
| Caesar&loretz,Phoenix     | Triamcinolone acetonide | 12173703   | 1       |
| Caelo                     | Triamcinolone acetonide | 12173704   | 2       |
| Caelo                     | Triamcinolone acetonide | 12173705   | 6       |
| Fagron                    | Triamcinolone acetonide | 12173705   | 1       |
| Caelo                     | Triamcinolone acetonide | 12173707   | 6       |
| Phönix 28.03.2013         | Triamcinolone acetonide | 12173707   | 1       |
| Caelo                     | Triamcinolone acetonide | 12173710   | 5       |
| Gehe                      | Triamcinolone acetonide | 122301508  | 1       |
| Caelo                     | Triamcinolone acetonide | 12301501   | 4       |
| Noweda                    | Triamcinolone acetonide | 12301501   | 1       |
| Caesar&loretz,Phoenix     | Triamcinolone acetonide | 12301502   | 1       |
| Caelo                     | Triamcinolone acetonide | 12301504   | 3       |
| Caelo                     | Triamcinolone acetonide | 12301503   | 1       |
| Fagron                    | Triamcinolone acetonide | 12301503   | 1       |
| Caelo                     | Triamcinolone acetonide | 12301506   | 1       |
| Noweda                    | Triamcinolone acetonide | 12301506   | 1       |
| Sanacorp                  | Triamcinolone acetonide | 12301506   | 1       |
| Caelo                     | Triamcinolone acetonide | 12301507   | 6       |
| Phoenix 11.03.2013        | Triamcinolone acetonide | 12301508   | 1       |
| Euro OTC                  | Triamcinolone acetonide | 12301507   | 1       |
| Caelo                     | Triamcinolone acetonide | 12301508   | 4       |
| Caelo                     | Triamcinolone acetonide | 12301509   | 5       |
| Caelo                     | Triamcinolone acetonide | 12301510   | 4       |
| Caelo                     | Triamcinolone acetonide | 12301515   | 16      |
| Otto Fischar              | Triamcinolone acetonide | 12301517   | 1       |

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| Supplier                   | Substance               | Batch            | Spectra |
|----------------------------|-------------------------|------------------|---------|
| Caelo                      | Triamcinolone acetonide | 12301518         | 4       |
| Ph.Eur.7,0                 | Triamcinolone acetonide | 12301518         | 1       |
| Noveda                     | Triamcinolone acetonide | 12301518         | 1       |
| Kehr                       | Triamcinolone acetonide | 1267708          | 1       |
| Fagron                     | Triamcinolone acetonide | 12B08-N01        | 7       |
| Fagron                     | Triamcinolone acetonide | 12B08N01         | 1       |
| Fagron                     | Triamcinolone acetonide | 12E15-N03        | 27      |
| Fagron                     | Triamcinolone acetonide | 12E15/N03        | 1       |
| Gehe                       | Triamcinolone acetonide | 12E15-N03        | 2       |
| Großhandel                 | Triamcinolone acetonide | 12E15-N03        | 1       |
| Noweda                     | Triamcinolone acetonide | 12E15-N03        | 1       |
| Caelo                      | Triamcinolone acetonide | 12E15-N03        | 2       |
| Phönix                     | Triamcinolone acetonide | 12E15-N03        | 1       |
| Euro OTC                   | Triamcinolone acetonide | 12G6008-01       | 1       |
| Fagron                     | Triamcinolone acetonide | 12I10-N09        | 6       |
| Hirsch                     | Triamcinolone acetonide | 12I10-N09        | 2       |
| Fagron                     | Triamcinolone acetonide | 12I10-N09        | 3       |
| Fagron                     | Triamcinolone acetonide | 13021408         | 1       |
| Euro OTC                   | Triamcinolone acetonide | 13030001-01      | 1       |
| Euro OTC                   | Triamcinolone acetonide | 13030001-02      | 1       |
| Euro OTC                   | Triamcinolone acetonide | 1303001-01       | 5       |
| Euro OTC                   | Triamcinolone acetonide |                  | 1       |
| Caelo                      | Triamcinolone acetonide | 1303001-02       | 2       |
| Gehe                       | Triamcinolone acetonide | 1303001-02       | 1       |
| Euro                       | Triamcinolone acetonide | 1303001-02       | 1       |
| Anzag                      | Triamcinolone acetonide | 1303001-02       | 1       |
| Newchem                    | Triamcinolone acetonide | 1303001-02       | 2       |
| Fagron                     | Triamcinolone acetonide | 13121201         | 1       |
| Euro OTC                   | Triamcinolone acetonide | 1307043-03       | 1       |
| Caelo                      | Triamcinolone acetonide | 1312407          | 1       |
| Caelo                      | Triamcinolone acetonide | 13124803         | 4       |
| Gehe                       | Triamcinolone acetonide | 13124803         | 1       |
| phönix                     | Triamcinolone acetonide | 13124803         | 1       |
| Gehe                       | Triamcinolone acetonide | 13124805         | 1       |
| Caelo                      | Triamcinolone acetonide | 13124806         | 3       |
| Sanacorp                   | Triamcinolone acetonide | 13124807         | 2       |
| Caesar & Loretz GmbH Hi... | Triamcinolone acetonide | 13124807         | 1       |
| noweda                     | Triamcinolone acetonide | 13256604         | 1       |
| Fagron                     | Triamcinolone acetonide | 13C13-20         | 1       |
| fargon                     | Triamcinolone acetonide | 13C13-N20        | 1       |
| Alliance Healthcare        | Triamcinolone acetonide | 13C13-N20        | 2       |
| Apotheke Mildena           | Triamcinolone acetonide | 13C13-N20        | 1       |
| Caelo                      | Triamcinolone acetonide | 13C13-N20        | 2       |
| Caelo                      | Triamcinolone acetonide | 13E15-N03        | 1       |
| Gehe                       | Triamcinolone acetonide | 13E15-N03        | 2       |
| Sanacorp                   | Triamcinolone acetonide | 13E15-N03        | 1       |
| Fagron                     | Triamcinolone acetonide | 13E15-No3        | 1       |
| Großhandel                 | Triamcinolone acetonide | 13E15-N03        | 1       |
| Gehe                       | Triamcinolone acetonide | 13I26-N11        | 1       |
|                            | Triamcinolone acetonide | 1403009-01       | 1       |
| Phönix                     | Triamcinolone acetonide | 14355703         | 1       |
| Fagron                     | Triamcinolone acetonide | 14K24N-N01       | 1       |
| Euro OTC                   | Triamcinolone acetonide | 150400701        | 1       |
| EuRho                      | Triamcinolone acetonide | 150800-08-02     | 1       |
| apoident                   | Triamcinolone acetonide | 1508008-01       | 1       |
| Fagron                     | Triamcinolone acetonide | 16011407         | 1       |
| Fagron                     | Triamcinolone acetonide | 15G31-B07-314046 | 1       |
| EuRho/Noweda               | Triamcinolone acetonide | 1601021-01       | 1       |
| Caelo                      | Triamcinolone acetonide | 1601312516       | 1       |
| Caelo                      | Triamcinolone acetonide | 1802212516       | 1       |

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| Supplier             | Substance               | Batch           | Spectra |
|----------------------|-------------------------|-----------------|---------|
| Fagron               | Triamcinolone acetonide | 20031302        | 1       |
| Caelo                | Triamcinolone acetonide | 2513M02516      | 1       |
| Euro OTC             | Triamcinolone acetonide | 20130912-5      | 1       |
| Fagron               | Triamcinolone acetonide |                 | 1       |
| Fagron               | Triamcinolone acetonide | 3212U-02516(NP) | 1       |
| Gehe                 | Triamcinolone acetonide | 700124-0007     | 1       |
| Fagron               | Triamcinolone acetonide | 411082-1-P      | 1       |
| Caelo                | Triamcinolone acetonide | 4613E2516       | 1       |
| Caelo                | Triamcinolone acetonide | 95/AKD34        | 1       |
| Caelo                | Triamcinolone acetonide | 93/AD1          | 1       |
| Audor Pharma         | Triamcinolone acetonide | APB0544/11101   | 2       |
| Audor Pharma         | Triamcinolone acetonide | APB0544/111010T | 3       |
| Europharm/Sanacorp   | Triamcinolone acetonide | B0544/111040    | 2       |
| Euro OTC             | Triamcinolone acetonide | B0544/111404    | 1       |
| Caelo                | Triamcinolone acetonide | Ch-B11267704    | 1       |
| Caelo                | Triamcinolone acetonide |                 | 1       |
| Fagron               | Triamcinolone acetonide | C22H25CIN209    | 1       |
| Fagron               | Triamcinolone acetonide | NS0571M         | 5       |
| Caelo                | Triamcinolone acetonide | NS0571M         | 1       |
| Fagron               | Triamcinolone acetonide | NS0996M         | 2       |
| Klenk                | Triamcinolone acetonide | NS1680M         | 1       |
| Fagron               | Triamcinolone acetonide | NS2571M         | 1       |
| Fagron               | Triamcinolone acetonide | NS0571M         | 1       |
| Euro OTC             | Triamcinolone acetonide | NV0635M         | 1       |
| Euro OTC             | Triamcinolone acetonide | NV2998M         | 1       |
| Caelo                | Triamcinolone acetonide | 9364422         | 1       |
| Oberlinden- Apotheke | Triamcinolone acetonide | U0544/113530    | 1       |
| Herbasinica          | Triamcinolone acetonide | 1110005-01      | 1       |
| Fagron               | Triamcinolone acetonide | 11N11-N10       | 1       |
| Fagron               | Triamcinolone acetonide | 1210-N09        | 1       |
| A.H.D.               | Triamcinolone acetonide | 12301508        | 1       |
| Euro OTC             | Triamcinolone acetonide | 130704301       | 1       |

- 68 300 spectra from 414 *Apo-Ident* customers from a total of 23 469 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Triamcinolone acetonide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Triamcinolone acetonide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 467           | 0              | 70 919        |
| <b>Type B</b> | 0              | 710           | 1              | 146 018       |
| <b>Type C</b> | 0              | 1300          | 33             | 68 300        |

The substance/substance group *Triamcinolone acetonide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.7152 %) |
| Type B | 100.0000 % (> 99.9923 %) | 99.8594 % (> 99.4374 %)  |
| Type C | 100.0000 % (> 99.8812 %) | 97.5244 % (> 97.2993 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20765     | 20765               | 0.00                         | 8.98                            |
| 20910     | 21061               | 4.21                         | 6.94                            |
| 21061     | 21061               | 0.00                         | 8.32                            |
| 21072     | 21061               | 1.71                         | 10.25                           |
| 21587     | 21587               | 0.00                         | 6.60                            |
| 21883     | 21883               | 0.00                         | 7.44                            |
| 21962     | 21587               | 4.20                         | 8.18                            |
| 22313     | 22313               | 0.00                         | 8.54                            |
| 22572     | 22572               | 0.00                         | 19.49                           |
| 22752     | 22752               | 0.00                         | 6.53                            |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Triclosan**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20005-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Triclosan; Triclosanum

### Special notes

When selecting the *Triclosan* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Triclosan*:

| Supplier | Substance | Batch      | Sample ID | Spectra | Certificate |
|----------|-----------|------------|-----------|---------|-------------|
| Caelo    | Triclosan | 13391808   | 21509     | 40      | 20131211    |
| Caelo    | Triclosan | 14121209   | 21591     | 40      | 20140718    |
| Euro OTC | Triclosan | 1406032-01 | 21615     | 40      | 20140710    |
| Euro OTC | Triclosan | 1507041    | 21856     | 40      | 20150804*   |
| Euro OTC | Triclosan | 1510045    | 22227     | 40      | 20150511*   |
| Euro OTC | Triclosan | 1602003    | 22373     | 30      | 20160204*   |
| Euro OTC | Triclosan | 1701032    | 22987     | 40      | 20170207*   |



## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 270 spectra of 7 reference samples from the substance/substance group *Triclosan*. These samples are listed above in the [calibration samples](#) section.
- 71 116 spectra from a total of 1545 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 406 spectra of 13 reference samples from the substance/substance group *Triclosan*.

| Supplier | Substance | Batch      | Sample ID          | Spectra |
|----------|-----------|------------|--------------------|---------|
| Caelo    | Triclosan | 83452249   | 20005              | 31      |
| Caelo    | Triclosan | 13391808   | 21509 <sup>†</sup> | 20      |
| Caelo    | Triclosan | 14121209   | 21591 <sup>†</sup> | 20      |
| Euro OTC | Triclosan | 1406032-01 | 21615 <sup>†</sup> | 20      |
| Euro OTC | Triclosan | 1507041    | 21856 <sup>†</sup> | 20      |
| Euro OTC | Triclosan | 1510045    | 22227 <sup>†</sup> | 20      |
| Euro OTC | Triclosan | 1602003    | 22373 <sup>†</sup> | 15      |
| Caelo    | Triclosan | 160846     | 22453              | 60      |
| Euro OTC | Triclosan | 1607002    | 22674              | 40      |
| Caelo    | Triclosan | 162808     | 22775              | 40      |
| Caelo    | Triclosan | 171498     | 23315              | 40      |
| Euro OTC | Triclosan | 1705011    | 23425              | 40      |
| Euro OTC | Triclosan | 1708025    | 23699              | 40      |

- 146 323 spectra from a total of 3181 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B*

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1721 spectra from 330 *Apo-Ident* customers from 335 batches from the substance/substance group *Triclosan*.

| Supplier                   | Substance | Batch      | Spectra |
|----------------------------|-----------|------------|---------|
| Fagron                     | Triclosan | 12L06-N01  | 38      |
| Fagron                     | Triclosan | 434083     | 1       |
| Fagron                     | Triclosan | 4394083    | 2       |
| Gehe                       | Triclosan | 4394083    | 1       |
| Fargon                     | Triclosan | 4394403    | 1       |
| BASF                       | Triclosan | 4486611    | 2       |
| Anzag/                     | Triclosan | 5846205    | 1       |
| Fagron                     | Triclosan | 5846205    | 2       |
| BASF Chem trade GmbH/Ph... | Triclosan | 5846205    | 1       |
| Fagron                     | Triclosan | 9000383    | 2       |
| BASF Grenzach/Noweda       | Triclosan | 5900346    | 1       |
| Fagron                     | Triclosan | 10006226   | 2       |
| Fagron                     | Triclosan | 106666066  | 1       |
| Fagron                     | Triclosan | 10666066   | 1       |
| BASF Grenzach GmbH/Phönix  | Triclosan | 10006226   | 1       |
| Fagron                     | Triclosan | 11777748   | 4       |
| Caelo                      | Triclosan | 11777748   | 2       |
| Rondell Apotheke           | Triclosan | 11965460   | 1       |
| Euro OTC                   | Triclosan | 12276023   | 1       |
| Fagron                     | Triclosan | 52/942     | 1       |
| Fagron                     | Triclosan | 6012014E   | 1       |
| Caelo                      | Triclosan | 8081401    | 1       |
| Caelo                      | Triclosan | 3041408    | 1       |
| Euro OTC                   | Triclosan | 1006024-01 | 1       |
| Fagron                     | Triclosan |            | 2       |
| Fagron                     | Triclosan | 10J18-N01  | 2       |
| Caelo                      | Triclosan | 10290812   | 1       |
| Fagron                     | Triclosan | 10112014C  | 1       |
| Caelo                      | Triclosan | 11/28-N02  | 1       |
| Gehe                       | Triclosan | 11/19-N11  | 1       |
| EuRho                      | Triclosan | 1107030-01 | 2       |
| Euro OTC                   | Triclosan | 1107030-01 | 4       |
| Caelo                      | Triclosan | 11076715   | 1       |
| Caelo                      | Triclosan | 11076716   | 1       |
| Caelo                      | Triclosan | 11076717   | 3       |
| Caelo                      | Triclosan | 11238002   | 1       |
| Caelo                      | Triclosan | 11238003   | 2       |
| Fagron                     | Triclosan | 11238004   | 1       |
| Caelo                      | Triclosan | 11238004   | 1       |
| Caelo                      | Triclosan | 11238009   | 2       |
| Caelo                      | Triclosan | 11238011   | 3       |
| Fagron                     | Triclosan | 11A05-N13  | 1       |
| Caelo                      | Triclosan | 11D20-N10  | 2       |
| Caelo                      | Triclosan | 1125204    | 1       |
| Fagron                     | Triclosan | 11D20-N10  | 3       |
| Caelo                      | Triclosan | 11238014   | 1       |
| Anzag am 24.05.2012        | Triclosan | 11d20-n10  | 1       |
| Caelo                      | Triclosan | 11d20-n10  | 1       |
| Fagron                     | Triclosan | 11H09-N02  | 9       |

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| <b>Supplier</b>       | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|-----------------------|------------------|--------------|----------------|
| Anzag                 | Triclosan        | 11H09-N02    | 1              |
| Gehe                  | Triclosan        | 11J28-N02    | 1              |
| Noweda                | Triclosan        | 11J28-N02    | 1              |
| Fagron                | Triclosan        | 11J28-N02    | 8              |
| Fagron                | Triclosan        | 11L19-N11    | 6              |
| Noweda                | Triclosan        | 11L19-N11    | 1              |
| Caelo                 | Triclosan        | 12003201     | 3              |
| DAB 2008              | Triclosan        | 12003201     | 2              |
| Phoenix               | Triclosan        | 12003202     | 1              |
| PHOENIX am 12.06.2012 | Triclosan        | 12003202     | 1              |
| Caelo                 | Triclosan        | 12003202     | 2              |
| Caelo                 | Triclosan        | 12003205     | 13             |
| Caelo                 | Triclosan        | 12003210     | 7              |
| EuRho                 | Triclosan        | 1202018-01   | 1              |
| Phönix                | Triclosan        | 1202018-01   | 2              |
| Euro OTC              | Triclosan        | 1202018-01   | 1              |
| Euro OTC              | Triclosan        | 1202018-02   | 2              |
| Euro OTC              | Triclosan        | 1206034-01   | 1              |
| Euro OTC              | Triclosan        | 1206034-02   | 3              |
| Euro OTC              | Triclosan        | 120203-02    | 1              |
| Phönix                | Triclosan        | 1206034-01   | 1              |
| Gehe                  | Triclosan        | 1206034-01   | 1              |
| Gehe                  | Triclosan        | 1206034-02   | 1              |
| Fagron                | Triclosan        | 1209213402   | 1              |
| Euro OTC              | Triclosan        | 1211025-01   | 11             |
| Caelo                 | Triclosan        | 12145901     | 5              |
| Caelo                 | Triclosan        | 1214510      | 1              |
| anzag, 26.11.2012     | Triclosan        | 12145902     | 1              |
| Caelo                 | Triclosan        | 12145902     | 5              |
| Caelo                 | Triclosan        | 12145906     | 7              |
| Mühlen-Apotheke       | Triclosan        | 12145906     | 1              |
| Caelo                 | Triclosan        | 12145907     | 12             |
| Caelo                 | Triclosan        | 12145908     | 8              |
| Phönix                | Triclosan        | 12145908     | 1              |
| Caelo                 | Triclosan        | 12145909     | 12             |
| Caelo                 | Triclosan        | 12145910     | 13             |
| Gehe                  | Triclosan        | 12145910     | 1              |
| Caesar/Lorenz         | Triclosan        | 12145910     | 1              |
| Caelo                 | Triclosan        | 12145917     | 1              |
| Caelo                 | Triclosan        | 12359104     | 6              |
| Fagron                | Triclosan        | 1214I03402   | 1              |
| Caesar/Lorenz         | Triclosan        | 12359104     | 1              |
| Gehe                  | Triclosan        | 12359104     | 1              |
| Caelo                 | Triclosan        | 12359105     | 11             |
| Sanacorp              | Triclosan        | 12359105     | 2              |
| Gehe                  | Triclosan        | 12359105     | 1              |
| Caelo                 | Triclosan        | 12359106     | 13             |
| Sanacorp              | Triclosan        | 12359106     | 1              |
| sana corp             | Triclosan        | 12359106     | 1              |
| Noweda                | Triclosan        | 12359107     | 1              |
| Caelo                 | Triclosan        | 12359107     | 1              |
| Caelo                 | Triclosan        | 12359108     | 12             |
| Caelo                 | Triclosan        | 12359109     | 6              |
| Phönix                | Triclosan        | 12359109     | 1              |
| Caelo                 | Triclosan        | 12359110     | 7              |
| Caelo                 | Triclosan        | 12359111     | 10             |
| Bombastus             | Triclosan        | 12359111     | 1              |
| Phönix, 02.08.2013    | Triclosan        | 12359111     | 1              |
| Phönix                | Triclosan        | 12359111     | 1              |
| Caelo                 | Triclosan        | 12359112     | 6              |

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| Supplier                    | Substance | Batch                | Spectra |
|-----------------------------|-----------|----------------------|---------|
| AHD, 02,12,13               | Triclosan | 12359112             | 1       |
| Gehe                        | Triclosan | 12359112             | 1       |
| anzag 20.11.2013            | Triclosan | 12359114             | 1       |
| Caelo                       | Triclosan | 12359114             | 1       |
| Gehe                        | Triclosan | 12359114             | 1       |
| Caelo                       | Triclosan | 12680801             | 1       |
| Caelo                       | Triclosan | 12c21-n05            | 1       |
| Euro OTC                    | Triclosan | 1245                 | 1       |
| Gehe                        | Triclosan | 12C21-N05            | 3       |
| Fagron                      | Triclosan | 12C21-N05            | 32      |
| Fagron                      | Triclosan | 12C21-n05            | 1       |
| Fagron                      | Triclosan | 12c21-n05            | 5       |
| FARGON                      | Triclosan | 12c21-n05            | 1       |
| Fiebig ek: 9,54EUR 31.08.12 | Triclosan | 12C21-N05            | 1       |
| Noweda                      | Triclosan | 12C21-N05            | 1       |
| Caelo                       | Triclosan | 12C21-N05            | 1       |
| Sino Phyto                  | Triclosan | 12C21-N05            | 1       |
| Fagron                      | Triclosan | 12d02-n02            | 1       |
| Fargon                      | Triclosan | 12C21-N05            | 1       |
| Anzag                       | Triclosan | 12G09-N09            | 2       |
| Fagron                      | Triclosan | 12C21-N05            | 1       |
| Fagron                      | Triclosan | 12G09-N09            | 6       |
| Alliance Healthcare         | Triclosan | 12G09-N09            | 1       |
| Fagron                      | Triclosan | 12G09-no9            | 1       |
| Fagron                      | Triclosan | 12G17-N04            | 33      |
| Fagron                      | Triclosan | 12G17-n04            | 1       |
| Caelo                       | Triclosan | 12G17-N04            | 2       |
| Anzag 4.12.12 ek:8,89       | Triclosan | 12G17-N04            | 1       |
| Großhandel                  | Triclosan | 12G17-N04            | 1       |
| Fargon                      | Triclosan | 12G17-N04            | 1       |
| Fagron                      | Triclosan | 12g17-n04            | 6       |
| fargon                      | Triclosan | 12G17-N04            | 1       |
| Fagron                      | Triclosan | 12G17N04             | 2       |
| Euro OTC                    | Triclosan | 12G17-N04            | 1       |
| Kehr                        | Triclosan | 12G17-N04            | 2       |
| Anzag                       | Triclosan | 12G17-N04            | 3       |
| Krieger                     | Triclosan | 12g17-N04            | 1       |
| Noweda                      | Triclosan | 12G17-N04            | 3       |
| Gehe                        | Triclosan | 12G17-N04            | 1       |
| Fagron                      | Triclosan | 12G17-No4            | 1       |
| Fagron                      | Triclosan | 12L06-0003           | 1       |
| Bombastus                   | Triclosan | 12L06-N01            | 2       |
| Anzag 18.04.13 ek: 8.89EUR  | Triclosan | 12L06N01             | 1       |
| Alliance Healthcare/Now...  | Triclosan | 12L06-N01            | 1       |
| Gehe                        | Triclosan | 12L06-n01            | 1       |
| Caelo                       | Triclosan | 12L06-N01            | 9       |
| Alliance Healthcare         | Triclosan | 12L06-N01            | 1       |
| Phönix                      | Triclosan | 12L06-N01            | 2       |
| GEHE                        | Triclosan | 12L06-N01            | 1       |
| Caelo                       | Triclosan | 12L06-n01            | 1       |
| Fagron                      | Triclosan | 12L06-n01            | 1       |
| Caelo                       | Triclosan | 12L06-N01/0005900346 | 1       |
| Fagron                      | Triclosan | 13/10-N02            | 1       |
| Fagron                      | Triclosan | 12L06-N01            | 1       |
| Euro OTC                    | Triclosan | 1303011-01           | 6       |
| Euro OTC                    | Triclosan | 1307050-01           | 5       |
| Euro OTC                    | Triclosan | 130301101            | 1       |
| EuRho/Phönix                | Triclosan | 1307050-01           | 2       |
| Noweda                      | Triclosan | 13247903             | 1       |
| Caelo                       | Triclosan | 13247903             | 1       |

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| Supplier                  | Substance | Batch              | Spectra |
|---------------------------|-----------|--------------------|---------|
| Caelo                     | Triclosan | 13247805           | 1       |
| Fagron                    | Triclosan | 13092012C          | 1       |
| Gehe                      | Triclosan | 13247903           | 1       |
| Caesar/Lorenz             | Triclosan | 13247904           | 1       |
| Caelo                     | Triclosan | 13247904           | 12      |
| Sanacorp                  | Triclosan | 13247904           | 2       |
| Caesar&Loretz GmbH/Anzag  | Triclosan | 13247904           | 2       |
| Caelo                     | Triclosan | 13247905           | 9       |
| phönix                    | Triclosan | 13247905           | 1       |
| Caerlo/Noweda             | Triclosan | 13247905           | 1       |
| Caelo                     | Triclosan | 13391801           | 2       |
| Caelo                     | Triclosan | 13391802           | 5       |
| Gehe                      | Triclosan | 13391804           | 2       |
| Caelo                     | Triclosan | 13391804           | 7       |
| GEHE 22.04.2014           | Triclosan | 13391804           | 1       |
| Sanacorp                  | Triclosan | 13391807           | 2       |
| Caelo                     | Triclosan | 13391807           | 7       |
| Phönix Gotha              | Triclosan | 13391807           | 1       |
| Caelo                     | Triclosan | 13391808           | 9       |
| Gehe                      | Triclosan | 13391811           | 1       |
| Fagron                    | Triclosan | 13a11n03           | 1       |
| Fagron                    | Triclosan | 13A11-N03          | 11      |
| Fagron                    | Triclosan | 13A11N03           | 1       |
| Gehe                      | Triclosan | 13A11-N03          | 1       |
| BASF Grenzach GmbH/Phönix | Triclosan | 13A11-N03          | 1       |
| Caelo                     | Triclosan | 13A11-N03          | 2       |
| Phönix                    | Triclosan | 13A11-N03          | 1       |
| BASF Grenzach GmbH/Phönix | Triclosan | 13A11-No3          | 1       |
| Fagron                    | Triclosan | 13A11-N03          | 1       |
| Fagron                    | Triclosan | 13D02-N02          | 81      |
| Caelo                     | Triclosan | 13D02-N02          | 7       |
| GEHE                      | Triclosan | 13D02-N02          | 2       |
| Gehe                      | Triclosan | 13D02-N02          | 3       |
| Fargon                    | Triclosan | 13D02-N02          | 2       |
| Fagron                    | Triclosan | 13D02N02           | 1       |
| Fischar/Gehe              | Triclosan | 13D02-N02          | 2       |
| AHC 02.09.13 EK9,04       | Triclosan | 13D02-N02          | 1       |
| Alliance Healthcare       | Triclosan | 13D02-N02          | 1       |
| BASF Grenzach GmbH/Phönix | Triclosan | 13D02-N02          | 1       |
| Euro OTC                  | Triclosan | 13D02-N02          | 1       |
| Fagron                    | Triclosan | 13d02-N02          | 1       |
| Fagron                    | Triclosan | 13D02-N-02         | 1       |
| Fragron                   | Triclosan | 13D02-N02          | 1       |
| Caelo                     | Triclosan | 13D02-No2          | 1       |
| Fagron                    | Triclosan | 13Do2-No2          | 2       |
| Sanacorp                  | Triclosan | 13D02-No2          | 1       |
| Fagron                    | Triclosan | 13D02-N02          | 1       |
| Europ Ots Pharma          | Triclosan | 13D02-N02          | 1       |
| Fagron                    | Triclosan | 13D02-N0Z          | 1       |
| Fagron                    | Triclosan | 13H08-N10          | 26      |
| Fagron                    | Triclosan | 13Do2-N02          | 1       |
| Fagron                    | Triclosan | 13H08N10           | 2       |
| Sanacorp                  | Triclosan | 13H08-N10          | 1       |
| Caelo                     | Triclosan | 13H08-N10          | 2       |
| Fagro/Gehe                | Triclosan | 13H08-N10          | 1       |
| Fagron                    | Triclosan | 13H08-N-10         | 1       |
| Euro OTC                  | Triclosan | 13H08-N10          | 1       |
| Fagron                    | Triclosan | 13H09-N01          | 72      |
| Fagron                    | Triclosan | 13H08-N100450/1231 | 1       |
| Caelo                     | Triclosan | 13H09-N01          | 10      |

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| Supplier                   | Substance | Batch             | Spectra |
|----------------------------|-----------|-------------------|---------|
| BASF Grenzach GmbH/Phönix  | Triclosan | 13H09-N01         | 1       |
| Alliance Healthcare/Fis... | Triclosan | 13H09-N01         | 1       |
| Fagron                     | Triclosan | 13H09N01          | 2       |
| Phönix                     | Triclosan | 13H09-N01         | 1       |
| Fagron                     | Triclosan | 13H09-No1         | 2       |
| Fagron                     | Triclosan | 13H09-N01         | 1       |
| Bombastus                  | Triclosan | 13L18-35-289984   | 1       |
| Fagron                     | Triclosan | 13J10-N02         | 1       |
| Fagron                     | Triclosan | 13L18-35-289995   | 1       |
| Phonix                     | Triclosan | 13L18-B35         | 1       |
| Fagron                     | Triclosan | 13L18-B35         | 12      |
| Alliance Healthcare        | Triclosan | 13L-18-835        | 1       |
| Fagron                     | Triclosan | 13L18-B35289995   | 1       |
| Fagron                     | Triclosan | 13L18-B35-289983  | 8       |
| Fagron                     | Triclosan | 13L18-B35-289     | 1       |
| Fagron                     | Triclosan | 13L18-B35-289984  | 3       |
| Raben-Apotheke Mildenau    | Triclosan | 13L18-B35-289984  | 2       |
| Fagron                     | Triclosan | 13L18-B35-289985  | 13      |
| Fagron                     | Triclosan | 13L18B35289984    | 1       |
| noweda                     | Triclosan | 13L18-B35-289985  | 1       |
| Fagron                     | Triclosan | 13L-18-B35-289985 | 1       |
| Phönix                     | Triclosan | 13L18-B35-289985  | 1       |
| Caelo                      | Triclosan | 13L18-B35-289985  | 1       |
| Fagron                     | Triclosan | 13L18-B35-289986  | 8       |
| Caelo                      | Triclosan | 13L18-B35-289986  | 2       |
| Caelo                      | Triclosan | 13L18B35289986    | 1       |
| Fagron                     | Triclosan | 13L18B35289987    | 1       |
| Fagron                     | Triclosan | 13L18-B35-289987  | 8       |
| Gehe                       | Triclosan | 13L18-B35-289987  | 1       |
| Fagron                     | Triclosan | 13L18-B35-289988  | 2       |
| Caelo                      | Triclosan | 13L18-B35-289987  | 1       |
| Caelo                      | Triclosan | 13L18-B35-289992  | 4       |
| Fagron                     | Triclosan | 13L18-B35-289992  | 2       |
| Caelo                      | Triclosan | 13L18B35289993    | 1       |
| AHD 17.01.15               | Triclosan | 13L18-B35-289992  | 1       |
| Fagron                     | Triclosan | 13L18-B35-289993  | 4       |
| Euro OTC                   | Triclosan | 13L18-B35-289993  | 1       |
| Fagron                     | Triclosan | 13L18B35-289993   | 1       |
| Fagron                     | Triclosan | 13L18-B35-289994  | 5       |
| Phönix                     | Triclosan | 13L18-B35-289995  | 2       |
| Fagron                     | Triclosan | 13L18-B35-289995  | 9       |
| Alliance Health 26.11.2... | Triclosan | 13L18-B35-289995  | 1       |
| Sonnenberg-Apotheke        | Triclosan | 13L18-B35-289995  | 1       |
| Euro OTC                   | Triclosan | 1401038-01        | 10      |
| Phönix                     | Triclosan | 13L8-B35          | 1       |
| Euro OTC                   | Triclosan | 140103801         | 1       |
| EuRho / 30                 | Triclosan | 1401038-01        | 1       |
| EuRho/Phoenix              | Triclosan | 1401038-01        | 1       |
| Fagron                     | Triclosan | 14022014C         | 1       |
| Caelo                      | Triclosan | 14052101          | 7       |
| Fagron                     | Triclosan | 1403217068        | 1       |
| Caelo                      | Triclosan | 14052102          | 12      |
| GEHE 17.06.2014            | Triclosan | 14052102          | 1       |
| Caelo                      | Triclosan | 14052103          | 17      |
| Caelo                      | Triclosan | 14052105          | 1       |
| Sanacorp                   | Triclosan | 14052103          | 1       |
| Gehe                       | Triclosan | 14052105          | 1       |
| Gehe                       | Triclosan | 1406032-01        | 1       |
| Euro OTC                   | Triclosan | 1406032-01        | 8       |
| Apomix/Noweda              | Triclosan | 1406032-01        | 2       |

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| Supplier                 | Substance | Batch             | Spectra |
|--------------------------|-----------|-------------------|---------|
| Euro OTC                 | Triclosan | 140603201         | 1       |
| Euro OTC                 | Triclosan | 1408024-01        | 6       |
| EuRho                    | Triclosan | 1408024-01        | 1       |
| Phönix Gotha             | Triclosan | 1408024-01        | 2       |
| Gehe                     | Triclosan | 1408024-01        | 1       |
| Noweda                   | Triclosan | 1408024-01        | 1       |
| Caelo                    | Triclosan | 14121203          | 8       |
| Caelo                    | Triclosan | 1412109           | 1       |
| Caelo                    | Triclosan | 14121204          | 7       |
| Euro OTC                 | Triclosan | 14121204          | 1       |
| Caelo                    | Triclosan | 14121207          | 12      |
| Phoenix 19.11.14         | Triclosan | 14121207          | 1       |
| ebe a                    | Triclosan | 14121207          | 1       |
| Caelo                    | Triclosan | 14121209          | 8       |
| Sana 06.11.14 EK 3,38    | Triclosan | 14121209          | 1       |
| Nowed 18.12.2014         | Triclosan | 14121210          | 2       |
| Caelo                    | Triclosan | 14121210          | 10      |
| Caelo                    | Triclosan | 14121211          | 7       |
| Sanacorp                 | Triclosan | 14121211          | 1       |
| Caelo                    | Triclosan | 14121214          | 10      |
| Caelo                    | Triclosan | 14121215          | 13      |
| Caesar&Loretz GmbH/Anzag | Triclosan | 14121215          | 2       |
| Sanacorp                 | Triclosan | 14121215          | 1       |
| Caelo                    | Triclosan | 14205901          | 6       |
| Caelo                    | Triclosan | 14121220          | 1       |
| Caelo                    | Triclosan | 14205902          | 7       |
| Caelo                    | Triclosan | 14205903          | 9       |
| Phoenix                  | Triclosan | 14205903          | 1       |
| Caelo                    | Triclosan | 14205904          | 6       |
| Caelo                    | Triclosan | 14205905          | 4       |
| Caelo                    | Triclosan | 14211211          | 1       |
| Caelo                    | Triclosan | 1425903           | 1       |
| Fagron                   | Triclosan | 14F23-B02         | 9       |
| Caelo                    | Triclosan | 14F23-B02         | 1       |
| Fagron                   | Triclosan | 14F23-B02-293852  | 2       |
| Caelo                    | Triclosan | 14f23-b02-29385   | 1       |
| Fagron                   | Triclosan | 14F23-B02-295756  | 2       |
| Caelo                    | Triclosan | 14F23B02293859    | 1       |
| Fagron                   | Triclosan | 14F23-B02-295757  | 3       |
| Fagron                   | Triclosan | 14f23-b02-295757  | 1       |
| Fagron                   | Triclosan | 14F23-B02-295758  | 8       |
| Fagron                   | Triclosan | 14f23-b02-295758  | 1       |
| Fagron                   | Triclosan | 14F23-B02-295759  | 8       |
| Allianc.Healthc../Apomix | Triclosan | 14F23-B02-295760  | 1       |
| Fagron                   | Triclosan | 14F23-B02-295760  | 7       |
| Fagron                   | Triclosan | 14F23-B02-295761  | 10      |
| Fagron                   | Triclosan | 14F23-B02-295762  | 2       |
| Fagron                   | Triclosan | 14F23-B02-295763  | 1       |
| Fagron                   | Triclosan | 14F23-B02-295764  | 2       |
| Fagron                   | Triclosan | 14F23B02295763    | 1       |
| Caelo                    | Triclosan | 14F23-B02-295765  | 1       |
| Fagron                   | Triclosan | 14F23-B02-295765  | 6       |
| Fagron                   | Triclosan | 14F23-B02-295947  | 6       |
| Cealo/AHD                | Triclosan | 14F23-B02-295947  | 1       |
| Fagron                   | Triclosan | 14F23-B02-295948  | 6       |
| Fagron                   | Triclosan | 14F23-B02-2959947 | 1       |
| Fagron                   | Triclosan | 14F23-B02-300219  | 6       |
| Fagron                   | Triclosan | 14F23B02300219    | 1       |
| Faron                    | Triclosan | 14F23-B02-300219  | 2       |
| Fagron                   | Triclosan | 14F23-Bo2-295947  | 1       |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|----------------------------|------------------|-------------------|----------------|
| Kremer/Phönix              | Triclosan        | 15/157/T          | 1              |
| Euro OTC                   | Triclosan        | 1501032-01        | 8              |
| Fagron                     | Triclosan        | 14F-B02-293859    | 1              |
| Phönix                     | Triclosan        | 14F23-Bo2-29575   | 1              |
| Euro OTC                   | Triclosan        | 1501032-02        | 4              |
| Caelo                      | Triclosan        | 1501032-02        | 1              |
| Euro OCT/Noweda            | Triclosan        | 1501032-02        | 1              |
| Euro OTC                   | Triclosan        | 1505009-01        | 9              |
| Euro OTC                   | Triclosan        | 150500901         | 1              |
| Sanacorp                   | Triclosan        | 1505009-01        | 1              |
| Fagron                     | Triclosan        | 1505009-01        | 1              |
| Caelo                      | Triclosan        | 1507041-01        | 1              |
| Euro OTC                   | Triclosan        | 1507041-01        | 5              |
| Euro OTC                   | Triclosan        | 1510045-01        | 12             |
| EuRho                      | Triclosan        | 151004501         | 1              |
| Euro UTC                   | Triclosan        | 1510045-01        | 1              |
| Caelo                      | Triclosan        | 15203603          | 14             |
| Caelo                      | Triclosan        | 15121202          | 1              |
| Noweda                     | Triclosan        | 15203603          | 2              |
| Sanacorp                   | Triclosan        | 151004501         | 1              |
| Caesar&Loretz GmbH/Anzag   | Triclosan        | 15203603          | 2              |
| Fagron                     | Triclosan        | 151010-B06-312984 | 1              |
| Caelo                      | Triclosan        | 15203604          | 8              |
| Fagron                     | Triclosan        | 15203604          | 1              |
| Noweda                     | Triclosan        | 15203604          | 1              |
| Caelo                      | Triclosan        | 15203606          | 8              |
| Caesar&lorenz,Phönix       | Triclosan        | 15203606          | 1              |
| Caelo                      | Triclosan        | 15203607          | 10             |
| caesar&lorenz,Phönix       | Triclosan        | 15203607          | 1              |
| Euro OTC                   | Triclosan        | 15203607          | 3              |
| Caesar & Loretz GmbH Hi... | Triclosan        | 15203607          | 1              |
| Caelo                      | Triclosan        | 15203608          | 4              |
| Caelo                      | Triclosan        | 1520603           | 1              |
| Caelo                      | Triclosan        | 15301502          | 7              |
| Caelo                      | Triclosan        | 15301501          | 1              |
| Caesar und Loretz          | Triclosan        | 15301502          | 1              |
| Caelo                      | Triclosan        | 15301503          | 6              |
| Caesar u Loretz            | Triclosan        | 15301503          | 1              |
| Caelo                      | Triclosan        | 15301504          | 9              |
| Caesar & Loretz GmbH Hi... | Triclosan        | 15301504          | 2              |
| Caelo                      | Triclosan        | 15301505          | 8              |
| Caesar&Loretz GmbH/Sana... | Triclosan        | 15301505          | 1              |
| Caelo                      | Triclosan        | 15301506          | 6              |
| Caelo                      | Triclosan        | 15301510          | 2              |
| Caelo                      | Triclosan        | 15301511          | 2              |
| Fagron                     | Triclosan        | 15301510          | 1              |
| Caelo                      | Triclosan        | 15301512          | 4              |
| Caelo                      | Triclosan        | 15301513          | 2              |
| Caelo                      | Triclosan        | 15301514          | 3              |
| Fagron                     | Triclosan        | 15C10-B06         | 6              |
| Phoenix                    | Triclosan        | 15C10-B06         | 1              |
| Fagron                     | Triclosan        | 15C10-B06-310031  | 3              |
| Fagron                     | Triclosan        | 15C10-B06-310032  | 2              |
| Fagron                     | Triclosan        | 15C10-B06-311161  | 9              |
| triclosan                  | Triclosan        | 15C10-B06-310032  | 1              |
| Fagron                     | Triclosan        | 15C10B06311161    | 2              |
| Fagron                     | Triclosan        | 15c10-B06-311161  | 1              |
| Fagron                     | Triclosan        | 15C10-B06-312980  | 2              |
| Caelo                      | Triclosan        | 15C10-B06-311161  | 1              |
| Fagron                     | Triclosan        | 15C10-B06-312981  | 11             |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|------------------|------------------|----------------|
| Fagron                     | Triclosan        | 15C10-B06-312982 | 11             |
| Euro OTC                   | Triclosan        | 15C10-B06-312981 | 1              |
| Caelo                      | Triclosan        | 15C10-B06-312982 | 3              |
| Fagron                     | Triclosan        | 15C10B06312982   | 1              |
| Fagron                     | Triclosan        | 15C10-B06-312983 | 5              |
| Fagron                     | Triclosan        | 15C10-Bo6-311161 | 1              |
| Fagron                     | Triclosan        | 15C10B06312983   | 1              |
| Fagron                     | Triclosan        | 15C-B06-312982   | 1              |
| Fagron                     | Triclosan        | 15G01-B03-310038 | 1              |
| Fagron                     | Triclosan        | 15G07-B03-310038 | 5              |
| Fagron                     | Triclosan        | 15G07-B03        | 3              |
| Fagron                     | Triclosan        | 15G07-B03-310035 | 2              |
| Fagron                     | Triclosan        | 15G07-B03-310036 | 1              |
| Caelo                      | Triclosan        | 15G07-B03-30039  | 1              |
| Caelo                      | Triclosan        | 15G07-B03-310037 | 1              |
| Fagron                     | Triclosan        | 15G07-B03-310037 | 8              |
| Fagron                     | Triclosan        | 15G07B03310037   | 1              |
| Fagron                     | Triclosan        | 15G07-B03-310039 | 1              |
| Hageda/Fargon              | Triclosan        | 15G07-B03-310038 | 1              |
| Caelo                      | Triclosan        | 15G07-B03-310038 | 1              |
| Fagron                     | Triclosan        | 15G07-B03-310040 | 4              |
| Fragron                    | Triclosan        | 15G07-B03-310040 | 1              |
| Euro OTC                   | Triclosan        | 15G07-B03-310040 | 1              |
| Euro OTC                   | Triclosan        | 1602003-01       | 14             |
| Caelo                      | Triclosan        | 160084601        | 1              |
| Fagron                     | Triclosan        | 15G07B03310040   | 1              |
| Euro OTC                   | Triclosan        | 160200301        | 1              |
| EuRhoNoweda                | Triclosan        | 1602003-01       | 1              |
| Caelo                      | Triclosan        | 16021306         | 1              |
| Euro OTC                   | Triclosan        | 1607002-01       | 11             |
| Caelo                      | Triclosan        | 16084601         | 5              |
| Euro OTC                   | Triclosan        | 160702-01        | 1              |
| Caelo                      | Triclosan        | 1607002-01       | 1              |
| Caelo                      | Triclosan        | 160846018        | 1              |
| Caelo                      | Triclosan        | 16084602         | 4              |
| Caelo                      | Triclosan        | 16084603         | 3              |
| Fagron                     | Triclosan        | 16084603         | 1              |
| Caelo                      | Triclosan        | 16084606         | 1              |
| Caesar & Loretz/AHC        | Triclosan        | 16084603         | 2              |
| Caelo                      | Triclosan        | 16084607         | 4              |
| Sanacorp                   | Triclosan        | 16084607         | 1              |
| Caelo                      | Triclosan        | 16084608         | 6              |
| Caelo                      | Triclosan        | 16084609         | 1              |
| Caesar&Loretz GmbH         | Triclosan        | 16084609         | 1              |
| Caelo                      | Triclosan        | 16084610         | 5              |
| Caelo                      | Triclosan        | 16084611         | 7              |
| Caelo                      | Triclosan        | 16084614         | 9              |
| Phoenix                    | Triclosan        | 16084614         | 1              |
| Fagron                     | Triclosan        | 16084614         | 1              |
| Euro OTC                   | Triclosan        | 16084614         | 1              |
| Caesar&Loretz,AHC,12.12... | Triclosan        | 16084618         | 1              |
| Caelo                      | Triclosan        | 16084618         | 4              |
| Euro OTC                   | Triclosan        | 1609005-01       | 8              |
| Euro OTC                   | Triclosan        | 1609005-02       | 3              |
| Caelo                      | Triclosan        | 16280801         | 10             |
| Gehe                       | Triclosan        | 16280801         | 2              |
| Caelo                      | Triclosan        | 16280802         | 5              |
| Caelo                      | Triclosan        | 16280803         | 2              |
| Caelo                      | Triclosan        | 16280805         | 1              |
| Gehe                       | Triclosan        | 16280808         | 1              |

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| <b>Supplier</b>    | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|--------------------|------------------|------------------|----------------|
| Caelo              | Triclosan        | 16280809         | 3              |
| Caelo              | Triclosan        | 16280808         | 3              |
| Caelo              | Triclosan        | 16280811         | 5              |
| Phönix             | Triclosan        | 16280811         | 2              |
| hochhaus-Apotheke  | Triclosan        | 16280811         | 1              |
| Caelo              | Triclosan        | 16280816         | 6              |
| Caelo              | Triclosan        | 16280817         | 4              |
| Caelo              | Triclosan        | 16280820         | 1              |
| Caelo              | Triclosan        | 16280824         | 1              |
| Euro/Phönix        | Triclosan        | 170103201        | 1              |
| Euro OTC           | Triclosan        | 1701032-01       | 2              |
| Gehe               | Triclosan        | 1701032-01       | 1              |
| Caelo              | Triclosan        | 17081704         | 1              |
| Caelo              | Triclosan        | 17081705         | 2              |
| Caelo              | Triclosan        | 17081707         | 9              |
| phoenix            | Triclosan        | 17081707         | 2              |
| Caelo              | Triclosan        | 17081710         | 2              |
| Caelo              | Triclosan        | 17081712         | 1              |
| Fagron             | Triclosan        | 17G07-B03-310038 | 1              |
| Fagron             | Triclosan        | 18082014B        | 1              |
| Caelo              | Triclosan        | 20021304         | 1              |
| Fagron             | Triclosan        | 200315B          | 1              |
| Caelo              | Triclosan        | 2213M-03402      | 1              |
| Caelo              | Triclosan        | 23121409         | 1              |
| Fagron             | Triclosan        | 190615A          | 1              |
| Fagron             | Triclosan        | 2513Q-03402      | 1              |
| Caelo              | Triclosan        | 2613Q-03402      | 1              |
| Sanacorp           | Triclosan        | 26/AKD1          | 1              |
| Sanacorp           | Triclosan        | 28/AKD4          | 1              |
| Fagron             | Triclosan        | 2914E-03402      | 1              |
| Fagron             | Triclosan        | 2901313402       | 1              |
| Caelo              | Triclosan        | 31/AKD7          | 1              |
| Caelo              | Triclosan        | 32/AKD13         | 1              |
| Caelo              | Triclosan        | 32/AKD11         | 1              |
| Caelo              | Triclosan        | 33/AKD1          | 1              |
| Caelo              | Triclosan        | 4212E-03402      | 1              |
| Caelo              | Triclosan        | 5012E-03402      | 1              |
| Caelo              | Triclosan        | 5203607          | 1              |
| Euro OTC           | Triclosan        | 700228           | 1              |
| Fagron             | Triclosan        | 700228-0005      | 1              |
| Caelo              | Triclosan        | AKD12            | 1              |
| Fagron             | Triclosan        | C12H7C1302       | 1              |
| Fagron             | Triclosan        | B03-310037       | 1              |
| Caelo              | Triclosan        |                  | 4              |
| Sanacorp           | Triclosan        |                  | 2              |
| Phoenix            | Triclosan        |                  | 1              |
| Euro OTC           | Triclosan        | CHB1303011-01    | 1              |
| Fagron             | Triclosan        | TCS0214037       | 1              |
| Fagro/Sanacorp     | Triclosan        | TCS0214037       | 1              |
| Gutenberg-Apotheke | Triclosan        | 13H09-N01        | 2              |
| Gutenberg-Apotheke | Triclosan        | 13L18-B35        | 1              |
| Beiersdorf         | Triclosan        | 14F23-B02-295764 | 1              |
| Fargon             | Triclosan        | 14F23-B02-295948 | 1              |
| Caeo/Noweda        | Triclosan        | 15301505         | 1              |
| Fagron             | Triclosan        | 15C10-B06-3161   | 1              |
| Anzag              | Triclosan        | 5846205          | 1              |
| Caelo              | Triclosan        | P144/14          | 1              |
| Gehe               | Triclosan        | 11/28-N02        | 1              |
| Herbasinica        | Triclosan        | 11d20-n10        | 1              |
| Gehe               | Triclosan        | 11D20-N10        | 1              |

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| Supplier        | Substance | Batch     | Spectra |
|-----------------|-----------|-----------|---------|
| Gehe            | Triclosan | 11H09-N02 | 1       |
| Fagron          | Triclosan | 12G09N09  | 1       |
| agron/ Noweda   | Triclosan | 13A11-N03 | 1       |
| Eigenproduktion | Triclosan | 13A11-N03 | 1       |
| A.H.D.          | Triclosan | 12L06-N01 | 1       |
| Sanacorp        | Triclosan | 13D02-N02 | 1       |
| Caelo           | Triclosan | 13H09-No1 | 1       |

- 67 912 spectra from 414 *Apo-Ident* customers from a total of 23 470 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Triclosan* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Triclosan* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 270           | 0              | 71 116        |
| <b>Type B</b> | 0              | 406           | 0              | 146 323       |
| <b>Type C</b> | 0              | 1684          | 37             | 67 912        |

The substance/substance group *Triclosan* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.7778 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.5222 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 97.8501 % (> 97.6758 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21509     | 22373               | 2.61                         | 61.62                           |
| 21591     | 22373               | 3.56                         | 61.74                           |
| 21615     | 22373               | 2.42                         | 62.55                           |
| 21856     | 21856               | 0.00                         | 61.07                           |
| 22227     | 22227               | 0.00                         | 59.98                           |
| 22373     | 22373               | 0.00                         | 61.33                           |
| 22987     | 22987               | 0.00                         | 59.71                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Trometamol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20004-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Trometamol; Trometamolum

### Special notes

When selecting the *Trometamol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Trometamol*:

| Supplier | Substance  | Batch     | Sample ID | Spectra | Certificate        |
|----------|------------|-----------|-----------|---------|--------------------|
| Fagron   | Trometamol | 13E22-N05 | 20856     | 40      | AR-17-FG-016395-01 |
| Caelo    | Trometamol | 14050002  | 21358     | 40      | 20140220           |
| Caelo    | Trometamol | 161688    | 22629     | 40      | 20160615*          |
| Caelo    | Trometamol | 16168810  | 23498     | 40      | 20160615           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Trometamol*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 110 spectra of 3 reference samples from the substance/substance group *Trometamol*.

| Supplier | Substance  | Batch            | Sample ID | Spectra |
|----------|------------|------------------|-----------|---------|
| Caelo    | Trometamol | 83303189         | 20004     | 30      |
| Fagron   | Trometamol | 17A16-B04-334121 | 23516     | 40      |
| Fagron   | Trometamol | 17A16-B04-334121 | 23517     | 40      |

- 146 619 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 378 spectra from 187 *Apo-Ident* customers from 102 batches from the substance/substance group *Trometamol*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier                   | Substance  | Batch            | Spectra |
|----------------------------|------------|------------------|---------|
| Caelo                      | Trometamol | 213E-02519       | 1       |
| Caelo                      | Trometamol | 313I-02519       | 1       |
| Caelo                      | Trometamol | 215I-02519       | 1       |
| Caelo                      | Trometamol | 314Q2519         | 1       |
| Fagron                     | Trometamol | 610I-02519       | 1       |
| Caelo                      | Trometamol | 914I-02519       | 1       |
| Caelo                      | Trometamol | 8031301          | 1       |
| Caelo                      | Trometamol | 1001312519       | 1       |
| Caelo                      | Trometamol |                  | 3       |
| Gehe                       | Trometamol | 11025103         | 1       |
| Caelo                      | Trometamol | 11160707         | 2       |
| Caesar & Loretz            | Trometamol | 11160707         | 1       |
| Gehe                       | Trometamol | 11160708         | 1       |
| Caelo                      | Trometamol | 11160711         | 1       |
| Caelo                      | Trometamol | 11160714         | 4       |
| Caesar & Loretz GmbH, 4... | Trometamol | 11160714         | 1       |
| GEHE                       | Trometamol | 11376005         | 1       |
| Caelo                      | Trometamol | 11376005         | 6       |
| Noweda                     | Trometamol | 11376005         | 1       |
| Caelo                      | Trometamol | 11376006         | 9       |
| Apotheke in Steinkuhl      | Trometamol | 120104/11        | 1       |
| Fagron                     | Trometamol | 11H08-N05        | 1       |
| Euro OTC                   | Trometamol | 1203005-02       | 2       |
| Caelo                      | Trometamol | 12113502         | 5       |
| Noweda                     | Trometamol | 12113502         | 1       |
| Caelo                      | Trometamol | 12113505         | 1       |
| Großhandel                 | Trometamol | 12113506         | 1       |
| Caelo                      | Trometamol | 12113506         | 10      |
| Sanacorp                   | Trometamol | 12113506         | 1       |
| Caelo                      | Trometamol | 12113510         | 1       |
| Caelo                      | Trometamol | 12113511         | 1       |
| Caelo                      | Trometamol | 12113508         | 1       |
| Caelo                      | Trometamol | 12113512         | 10      |
| Anzag                      | Trometamol | 12113512         | 1       |
| ANZAG                      | Trometamol | 12113512         | 1       |
| Phönix                     | Trometamol | 12113512         | 1       |
| Caelo                      | Trometamol | 12113515         | 5       |
| Fagron                     | Trometamol | 12E25-B40        | 1       |
| Fagron                     | Trometamol | 12I27-N03        | 2       |
| Fagron                     | Trometamol | 12I27-No3        | 2       |
| Fagron                     | Trometamol | 12k14n05         | 1       |
| Fagron                     | Trometamol | 12I27-N03        | 1       |
| Fagron                     | Trometamol | 12K14-N05        | 2       |
| Caelo                      | Trometamol | 12K14-N05        | 1       |
| Fagron                     | Trometamol | 13/19-B02-286158 | 3       |
| Phönix Gotha               | Trometamol | 13/19-B02-286158 | 1       |
| Fagron                     | Trometamol | 13/19-B02-293595 | 2       |
| Fagron                     | Trometamol | 13/19-B02        | 1       |
| Caelo                      | Trometamol | 13051401         | 1       |
| Fagron                     | Trometamol | 12k14no5         | 1       |
| Caelo                      | Trometamol | 13095901         | 9       |
| Gehe                       | Trometamol | 13095901         | 1       |
| Phönix 1. 07. 2013         | Trometamol | 13095901         | 1       |
| Caelo                      | Trometamol | 13095902         | 11      |
| Phönix, 02.08.2013         | Trometamol | 13095902         | 1       |
| Klenk                      | Trometamol | 13095902         | 3       |
| Caesar & Loretz GmbH, 4... | Trometamol | 13095902         | 1       |
| Caelo                      | Trometamol | 13095905         | 1       |
| Caelo                      | Trometamol | 13095910         | 5       |
| Caelo                      | Trometamol | 13095911         | 16      |

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| <b>Supplier</b>      | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|----------------------|------------------|------------------|----------------|
| Anzag                | Trometamol       | 13095911         | 1              |
| Caelo                | Trometamol       | 13095912         | 18             |
| Phönix               | Trometamol       | 13095912         | 2              |
| Sanacorp             | Trometamol       | 13095912         | 1              |
| Caelo                | Trometamol       | 13095913         | 3              |
| Caelo                | Trometamol       | 13095915         | 3              |
| Fagron               | Trometamol       | 13119-B02        | 1              |
| Caelo                | Trometamol       | 13339103         | 8              |
| Phönix Gotha         | Trometamol       | 1319-B02-286158  | 1              |
| Fagron               | Trometamol       | 13339103         | 1              |
| Caelo                | Trometamol       | 13339105         | 1              |
| Caelo                | Trometamol       | 13339107         | 6              |
| Caelo                | Trometamol       | 13339108         | 11             |
| Fagron               | Trometamol       | 13C08-N07        | 3              |
| Caelo                | Trometamol       | 1339103          | 1              |
| Caelo                | Trometamol       | 13C-08-N07       | 1              |
| Caelo                | Trometamol       | 13E22-N05        | 1              |
| Fagron               | Trometamol       | 13E22-N05        | 6              |
| Gehe                 | Trometamol       | 13E22-N05        | 1              |
| Fagron               | Trometamol       | 13I19-B02        | 1              |
| Fagron               | Trometamol       | 13I19-B02-286158 | 1              |
| Fagron               | Trometamol       | 13I19-B02-286158 | 1              |
| Caelo                | Trometamol       | 14050002         | 6              |
| Caelo                | Trometamol       | 14050003         | 3              |
| Caesar & Loretz GmbH | Trometamol       | 14050003         | 1              |
| Caelo                | Trometamol       | 14050004         | 3              |
| Caelo                | Trometamol       | 14332402         | 17             |
| Caelo                | Trometamol       | 14050006         | 1              |
| Phönix               | Trometamol       | 14332402         | 1              |
| Caelo                | Trometamol       | 14332403         | 1              |
| Fagron               | Trometamol       | 14F19-B03        | 1              |
| Caelo                | Trometamol       | 14332404         | 1              |
| Caelo                | Trometamol       | 14332409         | 1              |
| Fagron               | Trometamol       | 14F19-B03-304293 | 1              |
| Caelo                | Trometamol       | 15070304         | 11             |
| Caelo                | Trometamol       | 15070307         | 3              |
| Caelo                | Trometamol       | 15070308         | 18             |
| sanacoro             | Trometamol       | 15070308         | 1              |
| Caelo                | Trometamol       | 15070311         | 14             |
| Caelo                | Trometamol       | 15070309         | 1              |
| Caelo                | Trometamol       | 15094401         | 13             |
| Caelo                | Trometamol       | 15094404         | 1              |
| Caelo                | Trometamol       | 15277602         | 1              |
| Caelo                | Trometamol       | 15377602         | 13             |
| Sanacorp             | Trometamol       | 15377602         | 1              |
| Caelo                | Trometamol       | 15377605         | 1              |
| Caelo                | Trometamol       | 15377604         | 1              |
| Caelo                | Trometamol       | 15377607         | 6              |
| Caelo                | Trometamol       | 15377611         | 5              |
| Gehe                 | Trometamol       | 15377611         | 1              |
| Caelo                | Trometamol       | 16168810         | 4              |
| Caelo                | Trometamol       | 18081503         | 1              |
| Caelo                | Trometamol       | 23062015B        | 1              |
| Caelo                | Trometamol       | 26111201         | 1              |
| Caelo                | Trometamol       | 21082013A        | 1              |
| Caelo                | Trometamol       | 27111304         | 1              |
| Fagron               | Trometamol       | 286158           | 1              |
| Fagron               | Trometamol       | 294101           | 1              |
| Sanacorp             | Trometamol       | 3686G018         | 1              |
| Caelo                | Trometamol       | 5315I-02519      | 1              |

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| Supplier | Substance  | Batch       | Spectra |
|----------|------------|-------------|---------|
| Caelo    | Trometamol | 5012M-02519 | 1       |
| Fagron   | Trometamol | 8386E050    | 1       |
| Merck    | Trometamol | 8386F017    | 1       |
| Caelo    | Trometamol | 3713E-02519 | 1       |
| Fagron   | Trometamol | C4H11N03    | 1       |
| Sanacorp | Trometamol | 8386F030    | 1       |
| Phoenix  | Trometamol |             | 2       |
| Sanacorp | Trometamol |             | 1       |
| Caelo    | Trometamol | 12113507    | 3       |
| AHD      | Trometamol | 13095910    | 1       |

- 69 255 spectra from 414 *Apo-Ident* customers from a total of 23 701 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Trometamol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Trometamol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 110           | 0              | 146 619       |
| <b>Type C</b> | 0              | 375           | 3              | 69 255        |

The substance/substance group *Trometamol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 94.5455 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 99.2063 % (> 98.4127 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20856     | 20856               | 0.00                         | 32.06                           |
| 21358     | 22629               | 5.76                         | 29.02                           |
| 22629     | 22629               | 0.00                         | 29.68                           |
| 23498     | 22629               | 5.73                         | 30.18                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tropicamide**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20598-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tropicamide; Tropicamidum

### Special notes

When selecting the *Tropicamide* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tropicamide*:

| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate        |
|----------|-------------|------------------|-----------|---------|--------------------|
| Fagron   | Tropicamide | 14D23-B04-293294 | 21685     | 40      | AR-15-FG-001641-01 |
| Fagron   | Tropicamide | 16G19-B05-324829 | 22885     | 40      | 20160905           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Tropicamide*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 180 spectra of 5 reference samples from the substance/substance group *Tropicamide*.

| Supplier    | Substance   | Batch            | Sample ID          | Spectra |
|-------------|-------------|------------------|--------------------|---------|
| zu erfassen | Tropicamide | pending          | 20514              | 40      |
| Fagron      | Tropicamide | 12C26-N02        | 20598              | 40      |
| Fagron      | Tropicamide | 12C26-N02        | 20626              | 40      |
| Fagron      | Tropicamide | 14D23-B04-293294 | 21685 <sup>†</sup> | 20      |
| Fagron      | Tropicamide | 17D25-B07-336833 | 23506              | 40      |

- 146 549 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 22 spectra from 8 *Apo-Ident* customers from 17 batches from the substance/substance group *Tropicamide*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance   | Batch              | Spectra |
|----------|-------------|--------------------|---------|
| Fagron   | Tropicamide | 12C26-N02          | 1       |
| Fagron   | Tropicamide | 12B01-N02          | 1       |
| Fagron   | Tropicamide | 12F18-N06          | 4       |
| Fagron   | Tropicamide | 13A30-N06          | 1       |
| Fagron   | Tropicamide | 12104-n03          | 1       |
| Fagron   | Tropicamide | 13L31-B08-289830   | 1       |
| Phoenix  | Tropicamide | 14L04-B02          | 2       |
| Fagron   | Tropicamide | 14D23-B04          | 1       |
| Fagron   | Tropicamide | 14D23B04293294     | 1       |
| Fagron   | Tropicamide | 13L-31-B08-292075  | 1       |
| Fagron   | Tropicamide | 14104-b02-315694   | 1       |
| Gehe     | Tropicamide | 15F18-B04          | 1       |
| Fagron   | Tropicamide | 20021302           | 1       |
| Gehe     | Tropicamide | 15F-18B-04         | 1       |
| Fagron   | Tropicamide | 23071508           | 1       |
| Fagron   | Tropicamide | Ch12L04-N03        | 2       |
| Fagron   | Tropicamide | Ch13L31-B08-289830 | 1       |

- 69 611 spectra from 414 *Apo-Ident* customers from a total of 23 784 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tropicamide* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tropicamide* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 166           | 14             | 146 549       |
| <b>Type C</b> | 0              | 18            | 4              | 69 611        |

The substance/substance group *Tropicamide* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 92.2222 % (> 90.5556 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 81.8182 % (> 68.1818 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21685     | 21685               | 0.00                         | 42.80                           |
| 22885     | 21685               | 22.66                        | 41.24                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tyrosine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21574-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tyrosine; Tyrosinum

### Special notes

When selecting the *Tyrosine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tyrosine*:

| Supplier | Substance | Batch       | Sample ID | Spectra | Certificate |
|----------|-----------|-------------|-----------|---------|-------------|
| Fagron   | Tyrosine  | 13G24-N22   | 21574     | 40      | 1411030     |
| Euro OTC | Tyrosine  | L1401037-01 | 21586     | 40      | 20140217    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group *Tyrosine*. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 3 reference samples from the substance/substance group *Tyrosine*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Fagron   | Tyrosine  | 13G24-N22        | 21574 <sup>†</sup> | 20      |
| Euro OTC | Tyrosine  | L1401037-01      | 21586 <sup>†</sup> | 20      |
| Fagron   | Tyrosine  | 16B26-B01-322911 | 23533              | 40      |

- 146 649 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 4 spectra from 3 *Apo-Ident* customers from 4 batches from the substance/substance group *Tyrosine*.

| Supplier | Substance | Batch       | Spectra |
|----------|-----------|-------------|---------|
| Fagron   | Tyrosine  | 12H09-N09   | 1       |
| Euro OTC | Tyrosine  | L1210050-01 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



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| Supplier | Substance | Batch      | Spectra |
|----------|-----------|------------|---------|
| Euro OTC | Tyrosine  | L1401037   | 1       |
| Dr. Behr | Tyrosine  | WE14080018 | 1       |

- 69 629 spectra from 414 *Apo-Ident* customers from a total of 23 797 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tyrosine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tyrosine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 4             | 0              | 69 629        |

The substance/substance group *Tyrosine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8816 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21574     | 21574               | 0.00                         | 91.91                           |
| 21586     | 21574               | 11.11                        | 85.70                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Tyrothricin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20732-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Tyrothricin; Tyrothricinum

### Special notes

When selecting the *Tyrothricin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Tyrothricin*:

| Supplier | Substance   | Batch            | Sample ID | Spectra | Certificate        |
|----------|-------------|------------------|-----------|---------|--------------------|
| Fagron   | Tyrothricin | 12K14-N01        | 20732     | 40      | 1509178            |
| Fagron   | Tyrothricin | 12K14-N01        | 21683     | 40      | AR-15-FG-001172-01 |
| Fagron   | Tyrothricin | 14A23-B05-294146 | 21876     | 40      | AR-15-FG-015005-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Tyrothricin*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 146 spectra of 4 reference samples from the substance/substance group *Tyrothricin*.

| Supplier | Substance   | Batch            | Sample ID          | Spectra |
|----------|-------------|------------------|--------------------|---------|
| Fagron   | Tyrothricin | 12K14-N01        | 21683 <sup>†</sup> | 20      |
| Fagron   | Tyrothricin | 14A23-B05-294146 | 21876 <sup>†</sup> | 20      |
| Fagron   | Tyrothricin | 12K14-N01        | 21683SI            | 60      |
| Fagron   | Tyrothricin | 14A23-B05-294146 | 21876SI            | 46      |

- 146 583 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1 spectra from 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Tyrothricin*.

| Supplier | Substance   | Batch     | Spectra |
|----------|-------------|-----------|---------|
| Fagron   | Tyrothricin | 13A14-N04 | 1       |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 69 632 spectra from 414 *Apo-Ident* customers from a total of 23 800 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Tyrothricin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Tyrothricin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 129           | 17             | 146 583       |
| <b>Type C</b> | 0              | 1             | 0              | 69 632        |

The substance/substance group *Tyrothricin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 88.3562 % (> 86.3014 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8826 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20732     | 20732               | 0.00                         | 39.61                           |
| 21683     | 21683               | 0.00                         | 35.24                           |
| 21876     | 21876               | 0.00                         | 39.76                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe

mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Ubidecarenone**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20392-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Ubidecarenone; Ubidecarenonum

### Special notes

When selecting the *Ubidecarenone* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Ubidecarenone*:

| Supplier | Substance     | Batch      | Sample ID | Spectra | Certificate        |
|----------|---------------|------------|-----------|---------|--------------------|
| Euro OTC | Ubidecarenone | 1205029-01 | 21247     | 40      | 20121009           |
| Caelo    | Ubidecarenone | 14004504   | 21388     | 40      | AR-15-FG-009220-01 |
| Euro OTC | Ubidecarenone | 1605030    | 22696     | 40      | 20160623*          |
| Euro OTC | Ubidecarenone | 1703026    | 23127     | 40      | 20170406*          |
| Caelo    | Ubidecarenone | 17209402   | 23581     | 40      | 20170823           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Ubidecarenone*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 220 spectra of 6 reference samples from the substance/substance group *Ubidecarenone*.

| Supplier | Substance     | Batch            | Sample ID          | Spectra |
|----------|---------------|------------------|--------------------|---------|
| Fagron   | Ubidecarenone | 10H19-N10        | 20360              | 40      |
| Dr. Behr | Ubidecarenone | WE-11100005      | 20392              | 40      |
| Caelo    | Ubidecarenone | 14004504         | 21388 <sup>†</sup> | 20      |
| Fagron   | Ubidecarenone | 16G26-B01-331742 | 23161              | 40      |
| Caelo    | Ubidecarenone | 17209402         | 23580              | 40      |
| Caelo    | Ubidecarenone | 172094           | 23647              | 40      |

- 146 509 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 15 spectra from 7 *Apo-Ident* customers from 15 batches from the substance/substance group *Ubidecarenone*.

| Supplier             | Substance     | Batch            | Spectra |
|----------------------|---------------|------------------|---------|
| Fagron               | Ubidecarenone | 14H26-B04-298244 | 1       |
| Euro OTC             | Ubidecarenone | 1515M-07029      | 1       |
| Fagron               | Ubidecarenone | 16B10-B05        | 1       |
| Fagron               | Ubidecarenone | 16G26-B01        | 1       |
| Audor Pharma         | Ubidecarenone | APSZFQ150614C    | 1       |
| Audor Pharma         | Ubidecarenone | APSCFQ150614C    | 1       |
| Fagron               | Ubidecarenone | 10H19-N-10       | 1       |
| Cfm Oskar Tropitzsch | Ubidecarenone | 5300001          | 1       |
| Euro OTC             | Ubidecarenone | 1014E-07029      | 1       |
| Fagron               | Ubidecarenone | 14E12-B06-293861 | 1       |
| Euro OTC             | Ubidecarenone | 1403020-02       | 1       |
| Euro OTC             | Ubidecarenone | L1403020-01      | 1       |
| Euro OTC             | Ubidecarenone | 1104003-01       | 1       |
| Euro OTC             | Ubidecarenone | L1412004-01      | 1       |
| Euro OTC             | Ubidecarenone | 1205029-01       | 1       |

- 69618 spectra from 414 *Apo-Ident* customers from a total of 23786 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Ubidecarenone* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Ubidecarenone* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 212           | 8              | 146 509       |
| <b>Type C</b> | 0              | 12            | 3              | 69 618        |

The substance/substance group *Ubidecarenone* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 96.3636 % (> 95.0000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to

exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21247     | 23127               | 7.21                         | 54.83                           |
| 21388     | 21388               | 0.00                         | 53.59                           |
| 22696     | 22696               | 0.00                         | 53.58                           |
| 23127     | 23127               | 0.00                         | 54.37                           |
| 23581     | 23127               | 2.41                         | 52.72                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Urea**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20017-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Urea; Carbamidum; Urea pura; Ureum

### Special notes

When selecting the *Urea* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Urea*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Fagron   | Urea      | 12F25-N05        | 20712     | 40      | 20120724    |
| Euro OTC | Urea      | 1404024-01       | 21537     | 40      | 20140519    |
| Caelo    | Urea      | 15154103         | 22315     | 40      | 20150722    |
| Fagron   | Urea      | 14I18-B03-303581 | 22317     | 40      | 20141003    |
| Caelo    | Urea      | 161074           | 22466     | 40      | 20160509*   |

*continued on the next page*

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| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Caelo    | Urea      | 170216           | 23033     | 40      | 20170202*   |
| Caelo    | Urea      | 15154103         | 22315SI   | 40      | 20150722    |
| Fagron   | Urea      | 14I18-B03-303581 | 22317SI   | 40      | 20141003    |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 320 spectra of 8 reference samples from the substance/substance group *Urea*. These samples are listed above in the [calibration samples](#) section.
- 71066 spectra from a total of 1546 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 430 spectra of 14 reference samples from the substance/substance group *Urea*.

| Supplier | Substance | Batch            | Sample ID            | Spectra |
|----------|-----------|------------------|----------------------|---------|
| Caelo    | Urea      | 82374239         | 20017                | 30      |
| Euro OTC | Urea      | 1404024-01       | 21537 <sup>†</sup>   | 20      |
| Caelo    | Urea      | 15154103         | 22315 <sup>†</sup>   | 20      |
| Fagron   | Urea      | 14I18-B03-303581 | 22317 <sup>†</sup>   | 20      |
| Euro OTC | Urea      | 1601044          | 22376                | 40      |
| Caelo    | Urea      | 161074           | 22466 <sup>†</sup>   | 20      |
| Euro OTC | Urea      | 1604044          | 22552                | 40      |
| Euro OTC | Urea      | 1702023          | 23156                | 40      |
| Euro OTC | Urea      | 1707015          | 23535                | 40      |
| Caelo    | Urea      | 15154103         | 22315SI <sup>†</sup> | 20      |
| Fagron   | Urea      | 14I18-B03-303581 | 22317SI <sup>†</sup> | 20      |
| Euro OTC | Urea      | 1604044          | 22552SI              | 40      |
| Caelo    | Urea      | 170216           | 23033SI              | 40      |
| Euro OTC | Urea      | 1702023          | 23156SI              | 40      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 146 299 spectra from a total of 3184 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1427 spectra from 330 *Apo-Ident* customers from 253 batches from the substance/substance group *Urea*.

| Supplier                   | Substance | Batch         | Spectra |
|----------------------------|-----------|---------------|---------|
| Caelo                      | Urea      | 15154110      | 17      |
| Caelo                      | Urea      | 15154112      | 21      |
| Gehe,05.04.17, 5,30EUR     | Urea      | 16107412      | 1       |
| Caelo                      | Urea      | 13064215      | 23      |
| Anzag, 12.12.2012          | Urea      |               | 1       |
| PHOENIX 29.08.2014         | Urea      |               | 1       |
| Hirsch                     | Urea      | 810811        | 1       |
| Caelo                      | Urea      | 14107113      | 17      |
| Caelo                      | Urea      | 2324534       | 1       |
| Fagron                     | Urea      | 235/12I04-N06 | 1       |
| Caelo                      | Urea      | 314Q2544      | 1       |
| Caelo                      | Urea      | 5061410       | 1       |
| Euro OTC                   | Urea      | 72/14         | 1       |
| Caelo                      | Urea      |               | 9       |
| Caelo                      | Urea      | 9240908       | 1       |
| Euro OTC                   | Urea      | 1003024-02    | 2       |
| Caelo                      | Urea      | 10081208      | 1       |
| Caelo                      | Urea      | 10116         | 1       |
| Caelo                      | Urea      | 10169722      | 1       |
| Caelo                      | Urea      | 10169726      | 2       |
| Caelo                      | Urea      | 10169731      | 2       |
| Caelo                      | Urea      | 107063        | 1       |
| Fagron                     | Urea      | 10E31-N06     | 1       |
| Euro OTC                   | Urea      | 1110023-01    | 1       |
| Sanacorp                   | Urea      | 1110023-01    | 1       |
| Caelo                      | Urea      | 11120725      | 1       |
| Caelo                      | Urea      | 11150701      | 2       |
| Caelo                      | Urea      | 1113A-025     | 1       |
| Caelo                      | Urea      | 11150702      | 3       |
| Caelo                      | Urea      | 11150703      | 1       |
| Caesar&loretz,Phoenix      | Urea      | 11150713      | 1       |
| Caelo                      | Urea      | 11150713      | 1       |
| Caelo                      | Urea      | 11150714      | 2       |
| Noweda                     | Urea      | 11150714      | 1       |
| Caelo                      | Urea      | 11150721      | 4       |
| Bombastus                  | Urea      | 11150721      | 1       |
| Phönix Gotha               | Urea      | 11150721      | 1       |
| Caesar & Loretz GmbH 40... | Urea      | 11150722      | 1       |
| Caelo                      | Urea      | 11150722      | 4       |
| Caelo                      | Urea      | 11150725      | 4       |
| Noweda                     | Urea      | 11150725      | 1       |
| Caesar & Loretz GmbH, 4... | Urea      | 11150736      | 1       |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|----------------------------|------------------|--------------|----------------|
| Caelo                      | Urea             | 11150731     | 2              |
| Caelo                      | Urea             | 11150736     | 7              |
| Caelo                      | Urea             | 11150738     | 2              |
| Caesar&loretz,Anzag        | Urea             | 11150738     | 1              |
| Caelo                      | Urea             | 1150722      | 1              |
| Euro OTC                   | Urea             | 118900       | 1              |
| Fagron                     | Urea             | 11F24-N16    | 1              |
| Fagron                     | Urea             | 11C25-N01    | 1              |
| Fagron                     | Urea             | 11D-13-M04   | 1              |
| Sino Phyto                 | Urea             | 118900-0003  | 1              |
| Fagron                     | Urea             | 11H01-N08    | 2              |
| Anzag am 07.05.2012        | Urea             | 11H01-N08    | 1              |
| Caelo                      | Urea             | 12101301     | 1              |
| Caelo                      | Urea             | 12111801     | 7              |
| phönix,19.12.2012          | Urea             | 12111801     | 1              |
| Caelo                      | Urea             | 12111802     | 10             |
| Caelo                      | Urea             | 12111803     | 1              |
| Caesar & Loretz GmbH, 4... | Urea             | 12111804     | 1              |
| Beiersdorf                 | Urea             | 12111804     | 2              |
| Caelo                      | Urea             | 12111804     | 8              |
| Gehe                       | Urea             | 12111804     | 1              |
| Phönix Gotha               | Urea             | 12111806     | 2              |
| Caelo                      | Urea             | 12111806     | 8              |
| Caesar&loretz,Phoenix      | Urea             | 12111806     | 3              |
| Caelo                      | Urea             | 12111807     | 9              |
| Klenk                      | Urea             | 12111807     | 1              |
| Noweda                     | Urea             | 12111807     | 1              |
| Caesar&Loretz GmbH D-40... | Urea             | 12111808     | 2              |
| Caelo                      | Urea             | 12111808     | 12             |
| Sanacorp                   | Urea             | 12111808     | 2              |
| Caelo                      | Urea             | 12111809     | 14             |
| Phönix                     | Urea             | 12111809     | 1              |
| Phönix 22.04.2013          | Urea             | 12111809     | 1              |
| Caelo                      | Urea             | 1211181      | 1              |
| Caelo                      | Urea             | 12111810     | 15             |
| Caesar & Loretz GmbH, 4... | Urea             | 12111810     | 2              |
| Gehe                       | Urea             | 12111810     | 1              |
| Sanacorp                   | Urea             | 12111810     | 1              |
| Caelo                      | Urea             | 12111820     | 16             |
| Gehe                       | Urea             | 12111820     | 1              |
| Caelo                      | Urea             | 12111822     | 19             |
| Caesar & Loretz GmbH       | Urea             | 12111822     | 1              |
| Gehe                       | Urea             | 12111822     | 1              |
| Phönix                     | Urea             | 12111822     | 1              |
| GEHE                       | Urea             | 12111822     | 2              |
| Caesar & Loretz GmbH, 4... | Urea             | 12111822     | 1              |
| Caesar/Lorenz              | Urea             | 12111822     | 1              |
| Caesar/Noweda              | Urea             | 12111823     | 1              |
| Caelo                      | Urea             | 12111823     | 11             |
| Anzag 17.04.13 ek:6,84EUR  | Urea             | 12111823     | 1              |
| Alliance Healthcare        | Urea             | 12111823     | 1              |
| Caelo                      | Urea             | 12111826     | 8              |
| Caesar & Loretz GmbH, 4... | Urea             | 12111828     | 2              |
| Caelo                      | Urea             | 12111828     | 19             |
| Caesar u Loretz            | Urea             | 12111828     | 1              |
| Caelo                      | Urea             | 12111834     | 2              |
| Caelo                      | Urea             | 1211802      | 1              |
| Caelo                      | Urea             | 1211804      | 1              |
| Caelo                      | Urea             | 1211806      | 1              |
| Phönix Gotha               | Urea             | 1211806      | 1              |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|----------------------------|------------------|-------------------|----------------|
| Caelo                      | Urea             | 1211809           | 1              |
| Caelo                      | Urea             | 1211820           | 1              |
| Caelo                      | Urea             | 1211808           | 1              |
| Fagron                     | Urea             | 1211822           | 2              |
| Caelo                      | Urea             | 1211823           | 1              |
| Sanacorp                   | Urea             | 1212007           | 1              |
| Euro OTC                   | Urea             | 1212007-01        | 12             |
| Euro OTC                   | Urea             | 121200701         | 1              |
| Phönix Gotha               | Urea             | 1212007-01        | 1              |
| EuRho                      | Urea             | 1212007-01        | 1              |
| Phönix                     | Urea             | 1212007-01        | 1              |
| Euro OTC                   | Urea             |                   | 1              |
| Euro OTC                   | Urea             | 1212007-02        | 3              |
| Laborchemie Apolda/Jenn... | Urea             | 12345             | 1              |
| Caelo                      | Urea             | 123456            | 1              |
| Finze                      | Urea             | 1264              | 1              |
| Caelo                      | Urea             | 12C20-N05         | 1              |
| Fagron                     | Urea             | 12C20-N05         | 1              |
| Anzag, 10.12.2012          | Urea             | 12F25-N05         | 1              |
| Fagron                     | Urea             | 12F25-N05         | 4              |
| Fagron                     | Urea             | 12I04-N06         | 1              |
| Fagron                     | Urea             | 12I04-N06         | 1              |
| Caelo                      | Urea             | 12I04-N06         | 1              |
| Caelo                      | Urea             | 12L10-N08         | 1              |
| Fagron                     | Urea             | 12I10-n08         | 1              |
| Fagron                     | Urea             | 12L10-N08         | 5              |
| Fagron                     | Urea             | 13/17-1302-287602 | 1              |
| Fagron                     | Urea             | 13/17-B02-287602  | 2              |
| Caelo                      | Urea             | 13042015B         | 1              |
| Caelo                      | Urea             | 1306412           | 1              |
| Caelo                      | Urea             | 13064201          | 6              |
| Noweda/KremerGmbH          | Urea             | 13064201          | 1              |
| Phönix Gotha               | Urea             | 13064202          | 1              |
| Caelo                      | Urea             | 13064202          | 16             |
| Caelo                      | Urea             | 13064203          | 14             |
| Caesar &Loretz GmbH        | Urea             | 13064203          | 1              |
| Sanacorp                   | Urea             | 13064203          | 1              |
| Großhandel                 | Urea             | 13064203          | 1              |
| Caelo                      | Urea             | 13064206          | 21             |
| Anzag / Noweda             | Urea             | 13064206          | 1              |
| Caesar & Loretz GmbH, 4... | Urea             | 13064206          | 2              |
| Caesar & Loretz GmbH       | Urea             | 13064206          | 1              |
| Caelo                      | Urea             | 13064207          | 18             |
| Phönix                     | Urea             | 13064207          | 1              |
| Gehe                       | Urea             | 13064207          | 1              |
| Caesar/Noweda              | Urea             | 13064208          | 1              |
| Caelo                      | Urea             | 13064212          | 28             |
| Caesar & Loretz GmbH       | Urea             | 1306421           | 1              |
| Caesar & Loretz GmbH, 4... | Urea             | 13064212          | 3              |
| ADH, 04.11.2013            | Urea             | 13064212          | 1              |
| Caelo                      | Urea             | 13064213          | 7              |
| Caelo                      | Urea             | 13064214          | 16             |
| Sanacorp                   | Urea             | 13064215          | 1              |
| Phönix                     | Urea             | 13064215          | 1              |
| Gehe                       | Urea             | 13064215          | 1              |
| Caesar & Loretz GmbH Hi... | Urea             | 13064215          | 1              |
| Caelo                      | Urea             | 13064217          | 2              |
| Caesar&Loretz GmbH/Anzag   | Urea             | 13064217          | 1              |
| Caelo                      | Urea             | 13064221          | 10             |
| Caelo                      | Urea             | 13064223          | 29             |

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| Supplier                 | Substance | Batch            | Spectra |
|--------------------------|-----------|------------------|---------|
| Phönix                   | Urea      | 13064223         | 1       |
| Sanacorp                 | Urea      | 13064223         | 1       |
| Caesar & Loretz GmbH     | Urea      | 13064223         | 1       |
| Caelo                    | Urea      | 13064224         | 2       |
| Caelo                    | Urea      | 13064225         | 1       |
| Caelo                    | Urea      | 13064226         | 12      |
| Caelo                    | Urea      | 13064227         | 6       |
| Caelo                    | Urea      | 13064228         | 22      |
| Caelo                    | Urea      | 13064230         | 15      |
| Caelo                    | Urea      | 13064231         | 11      |
| Caelo/Phönix             | Urea      | 13064231         | 1       |
| Phoenix                  | Urea      | 13064231         | 1       |
| Caesar&Loretz GmbH/Anzag | Urea      | 13064231         | 1       |
| Caelo                    | Urea      | 13064232         | 17      |
| Gehe                     | Urea      | 13064232         | 1       |
| Caelo                    | Urea      | 13064233         | 19      |
| Caelo                    | Urea      | 13064236         | 8       |
| Phönix                   | Urea      | 13064236         | 1       |
| Euro OTC                 | Urea      | 13064239         | 1       |
| Caelo                    | Urea      | 13064239         | 2       |
| Caelo                    | Urea      | 13072015B        | 1       |
| Caelo                    | Urea      | 1317B02-287602   | 1       |
| Anzag/Henry Lamotte      | Urea      | 13-18-B03-303581 | 1       |
| Caelo                    | Urea      | 1364212          | 1       |
| Fagron                   | Urea      | 13D03-N01        | 9       |
| Phönix 19.06.2013        | Urea      | 13D03-N01        | 1       |
| Fagron                   | Urea      | 13D03-N001       | 1       |
| Dr. August Wolff         | Urea      | 13E17N02         | 1       |
| Fagron                   | Urea      | 13E17-N02        | 1       |
| Fagron                   | Urea      | 13E21-N05        | 4       |
| Caelo                    | Urea      | 13E21-N05        | 1       |
| Fagron                   | Urea      | 13J17-B02        | 2       |
| Fagron                   | Urea      | 13J17-B02-287602 | 2       |
| PHOENIX 02.05.2014       | Urea      | 13J17-B02-287602 | 2       |
| Fagron                   | Urea      | 13J17-B02-287604 | 7       |
| Fagron                   | Urea      | 13j17-B02-287604 | 1       |
| Raben-Apotheke Mildenau  | Urea      | 13J17-B02-287604 | 2       |
| Fagron                   | Urea      | 13J17B02-287604  | 1       |
| Fagron                   | Urea      | 13L20B03         | 1       |
| Fagron                   | Urea      | 13L20-B03289708  | 1       |
| Raben-Apotheke Mildenau  | Urea      | 13J17-Bo2-287604 | 1       |
| Fagron                   | Urea      | 13L20-B03-289708 | 5       |
| Fagron                   | Urea      | 13L20B03289708   | 1       |
| Caelo                    | Urea      | 14/18-B03-303581 | 2       |
| Fagron                   | Urea      | 14/18-B03-303581 | 4       |
| Fagron                   | Urea      | 14/18B03303581   | 1       |
| Euro OTC                 | Urea      | 1404024-01       | 21      |
| Caelo                    | Urea      | 14011513         | 1       |
| Eurho                    | Urea      | 1404024-01       | 1       |
| Phönix Gotha             | Urea      | 1404024-01       | 1       |
| Sanacorp                 | Urea      | 1405028-01       | 1       |
| Caelo                    | Urea      | 1410701          | 1       |
| Caelo                    | Urea      | 14107101         | 9       |
| Euro OTC                 | Urea      | 14107101         | 2       |
| Caesar&Loretz GmbH       | Urea      | 14107101         | 1       |
| Caelo                    | Urea      | 14107102         | 29      |
| Gehe                     | Urea      | 14107102         | 1       |
| Sanacorp                 | Urea      | 14107102         | 1       |
| Phönix                   | Urea      | 14107102         | 1       |
| Caelo                    | Urea      | 14107103         | 11      |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>      | <b>Spectra</b> |
|----------------------------|------------------|-------------------|----------------|
| Caelo                      | Urea             | 14107108          | 9              |
| Bombastus                  | Urea             | 14107108          | 1              |
| Euro OTC                   | Urea             | 14107108          | 1              |
| Caelo                      | Urea             | 14107109          | 20             |
| Phönix                     | Urea             | 14107109          | 1              |
| Ph.Eur.7.0                 | Urea             | 14107109          | 1              |
| Caelo                      | Urea             | 14107112          | 17             |
| Träger                     | Urea             | 14107112          | 1              |
| Sanacorp                   | Urea             | 14107112          | 1              |
| Caesar&Loretz GmbH /Anzag  | Urea             | 14107113          | 1              |
| Caelo                      | Urea             | 14107117          | 6              |
| Caelo                      | Urea             | 14107118          | 5              |
| Caelo                      | Urea             | 14107119          | 20             |
| Caelo                      | Urea             | 14107120          | 7              |
| Caelo                      | Urea             | 14107122          | 14             |
| Caelo                      | Urea             | 1417101           | 1              |
| Fagron                     | Urea             | 1418-B03-303581   | 1              |
| Fagron                     | Urea             | 1418b03303581     | 1              |
| Fagron                     | Urea             | 1418B03303581     | 1              |
| Caelo                      | Urea             | 14197118          | 1              |
| Fagron                     | Urea             | 14E07-B05         | 10             |
| Fagron                     | Urea             | 14E07B05          | 3              |
| Caelo                      | Urea             | 14E07-B05-289706  | 1              |
| Fagron                     | Urea             | 14E07-B05-289706  | 1              |
| Fagron                     | Urea             | 14E07-B05-293469  | 8              |
| Caelo                      | Urea             | 14E07-B05-293469  | 1              |
| AHD                        | Urea             | 14E07-B05-293469  | 1              |
| Fagron                     | Urea             | 14E-07-B05-293469 | 1              |
| Fargon/Alliance HC         | Urea             | 14E07-B05-293469  | 1              |
| Fagron                     | Urea             | 14E07B05293469    | 1              |
| Fagron                     | Urea             | 14E07-B05-297165  | 2              |
| Fagron                     | Urea             | 14E07-B05-297167  | 5              |
| Alliance health            | Urea             | 14E07-B05-297167  | 1              |
| Fagron                     | Urea             | 14E07-B07-293469  | 1              |
| Fagron                     | Urea             | 14E8900-0001      | 1              |
| Fagron                     | Urea             | 14I18-B03         | 4              |
| Caelo                      | Urea             | 14I18-B03         | 1              |
| Fagron                     | Urea             | 14I18-B03-303576  | 4              |
| Fagron                     | Urea             | 14I18-B03-303581  | 4              |
| Caelo                      | Urea             | 14I18-B03-303581  | 1              |
| Euro OTC                   | Urea             | 1503042-01        | 19             |
| Fagron                     | Urea             | 14118-B03         | 1              |
| Fagron                     | Urea             | 14118-B03-0303581 | 1              |
| Euro OTC                   | Urea             | 150304201         | 1              |
| Caelo                      | Urea             | 1508/104          | 1              |
| Caelo                      | Urea             | 15087102          | 4              |
| Caesar & Loretz GmbH       | Urea             | 15087103          | 1              |
| Caelo                      | Urea             | 15087103          | 16             |
| Phönix                     | Urea             | 15087103          | 1              |
| Caelo                      | Urea             | 15087104          | 14             |
| Caesar & Loretz GmbH       | Urea             | 15087105          | 1              |
| Caelo                      | Urea             | 15087105          | 12             |
| Caelo                      | Urea             | 15087107          | 14             |
| Phönix                     | Urea             | 15087110          | 3              |
| Caelo                      | Urea             | 15087110          | 18             |
| Caesar&Loretz GmbH /Anzag  | Urea             | 15087110          | 1              |
| Caelo                      | Urea             | 1514110           | 2              |
| Euro OTC                   | Urea             | 1515404           | 1              |
| Caelo                      | Urea             | 15154103          | 29             |
| Caesar & Loretz GmbH Hi... | Urea             | 15154103          | 1              |

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| Supplier                   | Substance | Batch             | Spectra |
|----------------------------|-----------|-------------------|---------|
| Euro OTC                   | Urea      | 15154103          | 1       |
| Caesar&Loretz/Caesar&Lo... | Urea      | 15154104          | 1       |
| Caelo                      | Urea      | 15154104          | 46      |
| Calo/AHD                   | Urea      | 15154104          | 1       |
| Caesar & Loretz GmbH       | Urea      | 15154104          | 1       |
| Fagron                     | Urea      | 15154104          | 2       |
| Castor/Phönix              | Urea      | 15154104          | 1       |
| Caelo                      | Urea      | 15154107          | 10      |
| Caelo                      | Urea      | 15154109          | 5       |
| Noweda                     | Urea      | 15154110          | 1       |
| Caelo                      | Urea      | 15154111          | 26      |
| Caesar&Loretz GmbH         | Urea      | 15154111          | 1       |
| Sanacorp                   | Urea      | 15154112          | 2       |
| Phoenix                    | Urea      | 15154113          | 1       |
| Caelo                      | Urea      | 15154113          | 10      |
| Phönix                     | Urea      | 15154113          | 1       |
| Caelo                      | Urea      | 15154116          | 4       |
| Caelo                      | Urea      | 1517E-02544       | 1       |
| Euro OTC                   | Urea      | 1601044-01        | 10      |
| Bombastus                  | Urea      | 1601044-01        | 1       |
| Caelo                      | Urea      | 1601044-01        | 2       |
| Caelo                      | Urea      | 160125/2          | 1       |
| Euro OTC                   | Urea      | 1604044-01        | 13      |
| Caelo                      | Urea      | 16107405          | 1       |
| Caelo                      | Urea      | 16107406          | 6       |
| Caelo                      | Urea      | 16107407          | 9       |
| Caelo                      | Urea      | 16107411          | 5       |
| Caesar&Loretz GmbH,Phön... | Urea      | 16107411          | 1       |
| Caelo                      | Urea      | 16107412          | 10      |
| Gehe                       | Urea      | 16107412          | 2       |
| Caelo                      | Urea      | 16107413          | 4       |
| Caelo                      | Urea      | 16107416          | 2       |
| Caelo                      | Urea      | 16107417          | 6       |
| Fagron                     | Urea      | 16D22-B02-3221532 | 1       |
| Fagron                     | Urea      | 16D22-B02         | 1       |
| Caelo                      | Urea      | 16107418          | 1       |
| Fagron                     | Urea      | 16D22-B02-322426  | 1       |
| Fagron                     | Urea      | 16D22-B02-322526  | 2       |
| Fagron                     | Urea      | 16D22-B02-322532  | 2       |
| Caelo                      | Urea      | 16D22-B02-322532  | 1       |
| Fagron                     | Urea      | 16D22B02322532    | 1       |
| Fagron                     | Urea      | 16D22-B02-326481  | 2       |
| Fagron                     | Urea      | 16I13-B02         | 1       |
| Fagron                     | Urea      | 16I13B02330166    | 1       |
| Euro OTC                   | Urea      | 1702023-01        | 1       |
| Caelo                      | Urea      | 17101310          | 1       |
| Caelo                      | Urea      | 17011405          | 1       |
| Caelo                      | Urea      | 18071301          | 1       |
| Fagron                     | Urea      | 18-B03-303581     | 1       |
| Caelo                      | Urea      | 20031514          | 1       |
| Caelo                      | Urea      | 20130912-4        | 1       |
| Fagron                     | Urea      | 2014162937        | 3       |
| Fagron                     | Urea      | 2014376618        | 1       |
| Fagron                     | Urea      | 2016142709        | 1       |
| Löns Apotheke              | Urea      | 20349             | 1       |
| Caelo                      | Urea      | 21051304          | 1       |
| Caelo                      | Urea      | 2109212544        | 1       |
| Caelo                      | Urea      | 22111305          | 1       |
| Caelo                      | Urea      | 25082015A         | 1       |
| Caelo                      | Urea      | 21111806          | 1       |

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| Supplier              | Substance | Batch            | Spectra |
|-----------------------|-----------|------------------|---------|
| Caelo                 | Urea      | 26071304         | 1       |
| Caelo                 | Urea      | 30031304         | 1       |
| Caelo                 | Urea      | 3012A-02544      | 1       |
| Caelo                 | Urea      | 3413Q-02544      | 1       |
| Fagron                | Urea      | 3613M-02544      | 1       |
| Löns Apotheke         | Urea      | 40003            | 1       |
| Caelo                 | Urea      | 4013Q2544        | 1       |
| Caelo                 | Urea      | 4111M-02544      | 1       |
| Caelo                 | Urea      | 4116M-02544      | 1       |
| Caelo                 | Urea      | 4914I-02544      | 1       |
| Caelo                 | Urea      | 5100             | 1       |
| Caelo                 | Urea      | 5208             | 1       |
| Caelo                 | Urea      | 62/AKD49         | 1       |
| Sanacorp              | Urea      | 62/AKD50s        | 1       |
| Caelo                 | Urea      | 568900           | 1       |
| Caelo                 | Urea      | 63/AKD4          | 1       |
| Caelo                 | Urea      | 82374179         | 2       |
| Caelo                 | Urea      | 64/AKD7          | 1       |
| Caelo                 | Urea      | AKD6             | 1       |
| Sanacorp              | Urea      |                  | 2       |
| Kehr                  | Urea      | CH4N2O           | 1       |
| Gutenberg-Apotheke    | Urea      |                  | 1       |
| test                  | Urea      | test             | 1       |
| Phönix Gotha          | Urea      | V096/2012        | 1       |
| Sanacorp              | Urea      | 63/AKD1          | 1       |
| Noweda                | Urea      | 13064223         | 1       |
| Noweda                | Urea      | 4109M-02544      | 1       |
| Sanacorp              | Urea      | 12111820         | 1       |
| Gehe                  | Urea      | 12111808         | 1       |
| Sanacorp              | Urea      | 13064212         | 1       |
| Caelo                 | Urea      | 1306422          | 1       |
| Gutenberg-Apotheke    | Urea      | 13064227         | 1       |
| VDL;05.02.15;10.15EUR | Urea      | 14107113         | 1       |
| Caelo                 | Urea      | 15144112         | 1       |
| Caelo                 | Urea      | 1610407          | 1       |
| Anzag                 | Urea      | 12111801         | 1       |
| GEHE                  | Urea      | 12111802         | 1       |
| Beiersdorf AG         | Urea      | 14/18-B03-303576 | 1       |
| Fargon                | Urea      | 14e07-b05-297165 | 1       |

- 68 206 spectra from 414 *Apo-Ident* customers from a total of 23 558 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Urea* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Urea* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 320           | 0              | 71 066        |
| Type B | 0              | 428           | 2              | 146 299       |
| Type C | 0              | 1406          | 21             | 68 206        |

The substance/substance group *Urea* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 98.1250 %) |
| Type B | 100.0000 % (> 99.9923 %) | 99.5349 % (> 98.8372 %)  |
| Type C | 100.0000 % (> 99.8812 %) | 98.5284 % (> 98.3181 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20712     | 22466               | 6.38                         | 68.88                           |
| 21537     | 22466               | 6.08                         | 70.35                           |
| 22315     | 23033               | 5.39                         | 67.70                           |
| 22317     | 22466               | 5.47                         | 68.27                           |
| 22466     | 22466               | 0.00                         | 69.09                           |
| 23033     | 23033               | 0.00                         | 68.80                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Uridine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20744-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Uridine; Uridinum

### Special notes

When selecting the *Uridine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Uridine*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Fagron   | Uridine   | 11G07-N04        | 20744     | 55      | 1402481     |
| Fagron   | Uridine   | 13K18-B31-288497 | 21895     | 40      | 20131129    |
| Audor    | Uridine   | APIB160018211AU  | 23529     | 40      | 20161118    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 135 spectra of 3 reference samples from the substance/substance group *Uridine*. These samples are listed above in the [calibration samples](#) section.
- 71 251 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 65 spectra of 3 reference samples from the substance/substance group *Uridine*.

| Supplier     | Substance | Batch            | Sample ID          | Spectra |
|--------------|-----------|------------------|--------------------|---------|
| Fagron       | Uridine   | 11G07-N04        | 20744 <sup>†</sup> | 5       |
| Fagron       | Uridine   | 13K18-B31-288497 | 21895 <sup>†</sup> | 20      |
| Audor Pharma | Uridine   | APIB1600169AU    | 23507              | 40      |

- 146 664 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 44 spectra from 22 *Apo-Ident* customers from 20 batches from the substance/substance group *Uridine*.

| Supplier | Substance | Batch     | Spectra |
|----------|-----------|-----------|---------|
| Fagron   | Uridine   | 12091402  | 1       |
| Fagron   | Uridine   | 11G07-N04 | 1       |

*continued on the next page*

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

continued from previous page

| Supplier               | Substance | Batch               | Spectra |
|------------------------|-----------|---------------------|---------|
| Caelo                  | Uridine   | 9129-N24            | 1       |
| Fagron                 | Uridine   | 13D08-N26           | 1       |
| Fagron                 | Uridine   | 13D29-N06           | 4       |
| Fagron                 | Uridine   | 13D29-N06           | 1       |
| Fagron                 | Uridine   | 13K18-B31           | 4       |
| Fagron                 | Uridine   | 14F02-B09           | 1       |
| Fagron                 | Uridine   | 14F02-B09-305467    | 7       |
| Fagron                 | Uridine   | 14051405            | 1       |
| siehe WE-Prüfprotokoll | Uridine   | 54/11               | 1       |
| Fagron                 | Uridine   | 22041301            | 1       |
| Fagron                 | Uridine   | 721110090           | 4       |
| Fagron                 | Uridine   | 16101301            | 1       |
| Fagron                 | Uridine   | 721010040           | 1       |
| Phönix                 | Uridine   | 721010040           | 1       |
| Sanacorp               | Uridine   | AP721060040/5U      | 1       |
| Audor Pharma           | Uridine   | AP721060040/5U      | 2       |
| Audor Pharma           | Uridine   | APIB1600182AU       | 1       |
| Audor Pharma           | Uridine   | APIB1400280AU       | 1       |
| Audor Pharma           | Uridine   | AP30514IB1500001AXU | 4       |
| Audor Pharma           | Uridine   | AP30514U            | 4       |

- 69 589 spectra from 414 *Apo-Ident* customers from a total of 23 781 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Uridine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Uridine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 135           | 0              | 71 251        |
| <b>Type B</b> | 0              | 65            | 0              | 146 664       |
| <b>Type C</b> | 0              | 43            | 1              | 69 589        |

The substance/substance group *Uridine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.5556 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.7692 %) |
| <b>Type C</b> | 100.0000 % (> 99.9813 %) | 97.7273 % (> 90.9091 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to

exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20744     | 20744               | 0.00                         | 36.20                           |
| 21895     | 20744               | 3.53                         | 35.88                           |
| 23529     | 20744               | 2.97                         | 36.73                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Valine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20405-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Valine; Valinum

### Special notes

When selecting the *Valine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Valine*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate |
|----------|-----------|------------------|-----------|---------|-------------|
| Fagron   | Valine    | 15A14-B07-307756 | 21953     | 40      | 9198        |
| Euro OTC | Valine    | 1604055          | 22571     | 40      | 20160601*   |
| Euro OTC | Valine    | 1701026          | 23131     | 40      | 20170222*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Valine*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 140 spectra of 4 reference samples from the substance/substance group *Valine*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Euro OTC | Valine    | L1006023-01      | 20405              | 40      |
| Fagron   | Valine    | 15A14-B07-307756 | 21953 <sup>†</sup> | 20      |
| Euro OTC | Valine    | 1609009          | 22799              | 40      |
| Euro OTC | Valine    | 1705017          | 23426              | 40      |

- 146 589 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 6 spectra from 5 *Apo-Ident* customers from 6 batches from the substance/substance group *Valine*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance | Batch       | Spectra |
|----------|-----------|-------------|---------|
| Euro OTC | Valine    | L1309029-01 | 1       |
| Fagron   | Valine    | 121259      | 1       |
| Euro OTC | Valine    | 1604055-01  | 1       |
| Euro OTC | Valine    | L1106045-01 | 1       |
| Fagron   | Valine    | 13B13-N05   | 1       |
| Euro OTC | Valine    | L1309029-02 | 1       |

- 69 627 spectra from 414 *Apo-Ident* customers from a total of 23 795 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Valine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Valine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 120           | 20             | 146 589       |
| <b>Type C</b> | 0              | 5             | 1              | 69 627        |

The substance/substance group *Valine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 85.7143 % (> 83.5714 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8815 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21953     | 21953               | 0.00                         | 62.12                           |
| 22571     | 22571               | 0.00                         | 65.76                           |
| 23131     | 23131               | 0.00                         | 61.32                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Vancomycin hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 21748-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Vancomycin hydrochloride; Vancomycini hydrochloridum

### Special notes

When selecting the *Vancomycin hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Vancomycin hydrochloride*:

| Supplier | Substance           | Batch          | Sample ID | Spectra | Certificate        |
|----------|---------------------|----------------|-----------|---------|--------------------|
| Euro OTC | Vancomycin hydro... | 1407047-01     | 21748     | 40      | AR-15-FG-008950-01 |
| Euro OTC | Vancomycin hydro... | 1506029        | 21826     | 40      | AR-15-FG-009077-01 |
| Euro OTC | Vancomycin hydro... | 1610038        | 22878     | 40      | 20161208*          |
| Audor    | Vancomycin hydro... | APHAP1609006EV | 23532     | 40      | AR-18-FG-000670-01 |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Vancomycin hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 280 spectra of 7 reference samples from the substance/substance group *Vancomycin hydrochloride*.

| Supplier | Substance                | Batch      | Sample ID          | Spectra |
|----------|--------------------------|------------|--------------------|---------|
| Euro OTC | Vancomycin hydrochloride | 1407047-01 | 21748 <sup>†</sup> | 20      |
| Euro OTC | Vancomycin hydrochloride | 1506029    | 21826 <sup>†</sup> | 20      |
| Euro OTC | Vancomycin hydrochloride | 1604037    | 22891              | 40      |
| Euro OTC | Vancomycin hydrochloride | 1407047-01 | 21748SI            | 60      |
| Euro OTC | Vancomycin hydrochloride | 1506029    | 21826SI            | 60      |
| Euro OTC | Vancomycin hydrochloride | 1610038    | 22878SI            | 40      |
| Euro OTC | Vancomycin hydrochloride | 1604037    | 22891SI            | 40      |

- 146 449 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *Vancomycin hydrochloride*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Vancomycin hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Vancomycin hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 175           | 105            | 146 449       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *Vancomycin hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 62.5000 % (> 61.4286 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21748     | 21748               | 0.00                         | 26.96                           |
| 21826     | 21826               | 0.00                         | 33.63                           |
| 22878     | 22878               | 0.00                         | 30.25                           |
| 23532     | 23532               | 0.00                         | 28.87                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Vanillin**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20204-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Vanillin; Vanillinum

### Special notes

When selecting the *Vanillin* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Vanillin*:

| Supplier | Substance | Batch     | Sample ID | Spectra | Certificate        |
|----------|-----------|-----------|-----------|---------|--------------------|
| Caelo    | Vanillin  | 14044413  | 21737     | 40      | 20140227           |
| Fagron   | Vanillin  | 13J01-N07 | 21738     | 40      | 20130926           |
| Caelo    | Vanillin  | 15135302  | 21924     | 40      | AR-17-FG-022168-03 |
| Caelo    | Vanillin  | 160895    | 22484     | 40      | 20160421*          |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Vanillin*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 8 reference samples from the substance/substance group *Vanillin*.

| Supplier | Substance | Batch     | Sample ID          | Spectra |
|----------|-----------|-----------|--------------------|---------|
| Fagron   | Vanillin  | 10L22-N17 | 20204              | 40      |
| Fagron   | Vanillin  | 7F29-N07  | 20217              | 40      |
| Caelo    | Vanillin  | 14044413  | 21737 <sup>†</sup> | 20      |
| Fagron   | Vanillin  | 13J01-N07 | 21738 <sup>†</sup> | 20      |
| Caelo    | Vanillin  | 15135302  | 21924 <sup>†</sup> | 20      |
| Caelo    | Vanillin  | 160895    | 22484 <sup>†</sup> | 20      |
| Caelo    | Vanillin  | 171172    | 23308              | 40      |
| Caelo    | Vanillin  | 17117201  | 23561              | 40      |

- 146 489 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

provided by the customer regarding manufacturer and batch number.

- 62 spectra from 51 *Apo-Ident* customers from 36 batches from the substance/substance group *Vanillin*.

| Supplier                   | Substance | Batch            | Spectra |
|----------------------------|-----------|------------------|---------|
| Fagron                     | Vanillin  | 314Q2548         | 1       |
| Dr.Hollborn                | Vanillin  | 6082015          | 1       |
| Caelo                      | Vanillin  | 10066811         | 1       |
| Fagron                     | Vanillin  | 8L05-N07         | 1       |
| Caesar & Loretz GmbH D-... | Vanillin  | 10066830         | 1       |
| Caelo                      | Vanillin  | 10066830         | 2       |
| Fagron                     | Vanillin  | 10L22-N17        | 1       |
| Fagron                     | Vanillin  | 11G28-N09        | 1       |
| Caesar & Loretz GmbH, 4... | Vanillin  | 12079401         | 1       |
| Caelo                      | Vanillin  | 112901           | 1       |
| Caesar & Loretz GmbH, 4... | Vanillin  | 12079412         | 1       |
| Caelo                      | Vanillin  | 12071401         | 1       |
| Gehe                       | Vanillin  | 12079412         | 1       |
| Caelo                      | Vanillin  | 12079412         | 3       |
| Caelo                      | Vanillin  | 12079417         | 1       |
| Caelo                      | Vanillin  | 12079428         | 1       |
| Caelo                      | Vanillin  | 12079424         | 1       |
| Rhodia GmbH/Noweda         | Vanillin  | 12D02-N03        | 1       |
| Fagron                     | Vanillin  | 12H09-N06        | 3       |
| Sanacorp                   | Vanillin  | 12H09-N06        | 1       |
| Caelo                      | Vanillin  | 12h09-n06        | 1       |
| fargron                    | Vanillin  | 13/01-N07        | 1       |
| Hedinger/Ebert             | Vanillin  | 13A30-N10        | 1       |
| Fagron                     | Vanillin  | 12Ko7-N19        | 1       |
| Fagron                     | Vanillin  | 13I01-N07        | 1       |
| Fagron                     | Vanillin  | 13J01-N07        | 6       |
| Caelo                      | Vanillin  | 14044419         | 1       |
| Fagron                     | Vanillin  | 14G02-B99-296988 | 1       |
| Caelo                      | Vanillin  | 15135302         | 2       |
| Caelo                      | Vanillin  |                  | 1       |
| Caelo                      | Vanillin  | 15154006         | 1       |
| Caelo                      | Vanillin  | 15154014         | 2       |
| Caelo                      | Vanillin  | 15154020         | 6       |
| Caelo                      | Vanillin  | 16089501         | 1       |
| Caelo                      | Vanillin  | 16089506         | 4       |
| Gehe                       | Vanillin  | 16089506         | 1       |
| Caelo                      | Vanillin  | 90961269         | 1       |
| Fagron                     | Vanillin  | 232050-0004      | 1       |
| Caelo                      | Vanillin  | 12079407         | 1       |
| Fagron                     | Vanillin  | 13/01-N07        | 1       |
| Caelo                      | Vanillin  | 15154017         | 1       |
| Caelo                      | Vanillin  | 14044404         | 1       |

- 69 571 spectra from 414 *Apo-Ident* customers from a total of 23 766 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Vanillin* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Vanillin* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 160           | 0              | 71 226        |
| Type B | 0              | 240           | 0              | 146 489       |
| Type C | 0              | 60            | 2              | 69 571        |

The substance/substance group *Vanillin* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| Type B | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| Type C | 100.0000 % (> 99.8813 %) | 96.7742 % (> 91.9355 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21737     | 21924               | 3.80                         | 29.75                           |
| 21738     | 22484               | 3.73                         | 29.63                           |
| 21924     | 21924               | 0.00                         | 28.24                           |
| 22484     | 22484               | 0.00                         | 30.50                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

IdentModul 1.3-2018-01

Validated substance/substance group **Waxes / Fats**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20747-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

## Relevant substance names

Waxes / Fats; Adeps solidus; Adeps solidus W35; Cacao oleum; Cera alba; Cera flava; Cetyl palmitate 15; Cetyl palmitas 15; Cetylum palminicum 15; Cocoa butter; Hard fat in pastilles; Hard fat W35; Natrii laurylsulfuricum; Oleum cacao; Paraffin, hard; Paraffin, microcrystalline; Paraffinum durum in rotulis; Paraffinum microcrystallinum; Paraffinum solidum in rotulis; Sodium dodecyl sulfate; Sodium dodecyl sulphate; Wax, bleached; Wax, yellow

## Special notes

When selecting the *Waxes / Fats* substance/substance group, the following information is displayed to the user:

*no information*

## Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

## Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

## Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Waxes / Fats*:

| Supplier | Substance     | Batch      | Sample ID | Spectra | Certificate |
|----------|---------------|------------|-----------|---------|-------------|
| Spinnrad | Wax, bleached | 1012402004 | 20747     | 40      | 20121101    |

*continued on the next page*

continued from previous page

| Supplier  | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|-----------|---------------------|------------------|-----------|---------|--------------------|
| Caelo     | Cetyl palmitate 15  | 12331916         | 20865     | 40      | 1402429            |
| Caelo     | Sodium dodecyl s... | 13099011         | 20986     | 40      | 1403108            |
| Caelo     | Hard fat in past... | 12158122         | 21067     | 40      | 20120627           |
| Caelo     | Wax, yellow         | 13335507         | 21433     | 40      | 20131011           |
| Caelo     | Cocoa butter        | 13292013         | 21482     | 40      | 20130924           |
| Caelo     | Wax, bleached       | 13378619         | 21483     | 20      | 1509364            |
| Caelo     | Paraffin, microc... | 14307104         | 21682     | 40      | AR-15-FG-005277-01 |
| Caelo     | Paraffin, hard      | 13390413         | 21731     | 40      | 20131213           |
| Caelo     | Paraffin, microc... | 14307106         | 21766     | 40      | 20141014           |
| Caelo     | Cetyl palmitate 15  | 14351606         | 21875     | 40      | 20141219           |
| Fagron    | Hard fat W35        | 15A07-B12-302751 | 21880     | 40      | 1604639            |
| Caelo     | Cetyl palmitate 15  | 15301703         | 21984     | 40      | AR-16-FG-007435-01 |
| Caelo     | Wax, bleached       | 14336620         | 22244     | 40      | 20141125           |
| Caelo     | Wax, yellow         | 15317602         | 22245     | 40      | 20151007           |
| Caelo     | Cetyl palmitate 15  | 15301703         | 22325     | 40      | 20151013           |
| Caelo     | Paraffin, microc... | 154128           | 22330     | 40      | 20160112*          |
| Fagron    | Hard fat W35        | 15A07-B12-309245 | 22338     | 40      | 20150115           |
| Caelo     | Cocoa butter        | 14348906         | 22348     | 40      | 20150122           |
| Caelo     | Paraffin, hard      | 15232004         | 22349     | 40      | 1702507            |
| Caelo     | Sodium dodecyl s... | 15344503         | 22352     | 40      | 20151022           |
| Caelo     | Hard fat in past... | 160278           | 22479     | 40      | 20160407*          |
| Caelo     | Cetyl palmitate 15  | 160538           | 22486     | 40      | 20160323*          |
| Caelo     | Wax, yellow         | 162750           | 22767     | 40      | 2061007*           |
| Caelo     | Wax, bleached       | 15292022         | 22956     | 40      | 20150827           |
| Caelo     | Cocoa butter        | 163165           | 23067     | 40      | 20161116*          |
| Caelo     | Sodium dodecyl s... | 16229217         | 23242     | 40      | 20160809           |
| Caelo     | Sodium dodecyl s... | 170955           | 23278     | 40      | 20170503*          |
| Bombastus | Hard fat in past... | 306363           | 23565     | 34      | 20161213           |
| Fagron    | Hard fat W35        | 16K08-B10-334910 | 23601     | 40      | 20161229           |
| Caelo     | Cocoa butter        | 17055907         | 23707     | 33      | 20170310           |

## Validation samples

A total of 287748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 1207 spectra of 31 reference samples from the substance/substance group *Waxes / Fats*. These samples are listed above in the [calibration samples](#) section.
- 70179 spectra from a total of 1522 batches from further 366 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 1413 spectra of 45 reference samples from the substance/substance group *Waxes / Fats*.

| Supplier    | Substance                  | Batch            | Sample ID          | Spectra |
|-------------|----------------------------|------------------|--------------------|---------|
| Caelo       | Wax, yellow                | 83038199         | 20033              | 30      |
| Caelo       | Cocoa butter               | 81070139         | 20035              | 70      |
| Caelo       | Hard fat in pastilles      | 10158804         | 20174              | 40      |
| Caelo       | Sodium dodecyl sulfate     | 10229510         | 20237              | 40      |
| Caelo       | Wax, yellow                | 11285001         | 20338              | 40      |
| Caelo       | Hard fat in pastilles      | 9318225          | 20339              | 40      |
| Caelo       | Paraffin, microcrystalline | 11100708         | 20400              | 40      |
| Caelo       | Paraffin, hard             | 11166916         | 20461              | 40      |
| Caelo       | Paraffin, hard             | 11166911         | 20532              | 40      |
| Caelo       | Wax, bleached              | 10364838         | 20610              | 40      |
| zu erfassen | Cocoa butter               | pending          | 21014              | 40      |
| zu erfassen | Cocoa butter               | pending          | 21015              | 40      |
| Caelo       | Cetyl palmitate 15         | 13295919         | 21316              | 20      |
| Caelo       | Wax, yellow                | 13335507         | 21433 <sup>†</sup> | 20      |
| Caelo       | Sodium dodecyl sulfate     | 13411305         | 21465              | 60      |
| Caelo       | Cetyl palmitate 15         | 13295919         | 21522              | 40      |
| Caelo       | Paraffin, microcrystalline | 14307104         | 21682 <sup>†</sup> | 20      |
| Caelo       | Paraffin, hard             | 13390413         | 21731 <sup>†</sup> | 20      |
| Caelo       | Paraffin, microcrystalline | 14307106         | 21766 <sup>†</sup> | 20      |
| Caelo       | Cetyl palmitate 15         | 14351606         | 21875 <sup>†</sup> | 20      |
| Fagron      | Hard fat W35               | 15A07-B12-302751 | 21880 <sup>†</sup> | 20      |
| Caelo       | Cetyl palmitate 15         | 15301703         | 21984 <sup>†</sup> | 20      |
| Caelo       | Wax, bleached              | 14336620         | 22244 <sup>†</sup> | 20      |
| Caelo       | Wax, yellow                | 15317602         | 22245 <sup>†</sup> | 20      |
| Caelo       | Cetyl palmitate 15         | 15301703         | 22325 <sup>†</sup> | 20      |
| Caelo       | Paraffin, microcrystalline | 154128           | 22330 <sup>†</sup> | 20      |
| Fagron      | Hard fat W35               | 15A07-B12-309245 | 22338 <sup>†</sup> | 20      |
| Caelo       | Cocoa butter               | 14348906         | 22348 <sup>†</sup> | 20      |
| Caelo       | Paraffin, hard             | 15232004         | 22349 <sup>†</sup> | 20      |
| Caelo       | Sodium dodecyl sulfate     | 15344503         | 22352 <sup>†</sup> | 20      |
| Caelo       | Hard fat in pastilles      | 160278           | 22479 <sup>†</sup> | 20      |
| Caelo       | Cetyl palmitate 15         | 160538           | 22486 <sup>†</sup> | 20      |
| Caelo       | Wax, bleached              | 161631           | 22587              | 40      |
| Fagron      | Hard fat W35               | 15J08-B04-324959 | 22806              | 40      |
| Caelo       | Paraffin, hard             | 16277704         | 23190              | 40      |
| Caelo       | Sodium dodecyl sulfate     | 16229205         | 23243              | 40      |
| Klenk       | Wax, yellow                | 290A170314       | 23511              | 40      |
| Caelo       | Wax, yellow                | 17011602         | 23512              | 40      |
| Caelo       | Wax, bleached              | 16163109         | 23513              | 40      |
| Caelo       | Cetyl palmitate 15         | 17043503         | 23560              | 40      |
| Bombastus   | Hard fat in pastilles      | 306363           | 23565 <sup>†</sup> | 6       |
| Caelo       | Cetyl palmitate 15         | 171640           | 23639              | 40      |
| Caelo       | Sodium dodecyl sulfate     | 172363           | 23664              | 40      |
| Bombastus   | Hard fat in pastilles      | 308558           | 23705              | 40      |
| Caelo       | Cocoa butter               | 17055907         | 23707 <sup>†</sup> | 7       |

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.



- 145 316 spectra from a total of 3153 batches from further 854 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 1526 spectra from 245 *Apo-Ident* customers from 522 batches from the substance/substance group *Waxes / Fats*.

| Supplier  | Substance             | Batch               | Spectra |
|-----------|-----------------------|---------------------|---------|
| Caelo     | Hard fat in pastilles | 14126203            | 6       |
| Caelo     | Hard fat in pastilles | 16027801            | 3       |
| Caelo     | Hard fat in pastilles | 16274201            | 5       |
| Caelo     | Hard fat in pastilles | P182/14             | 1       |
| Caelo     | Hard fat in pastilles | 11109616            | 1       |
| Caelo     | Hard fat in pastilles | 11345905            | 4       |
| Caelo     | Hard fat in pastilles | 13243301            | 5       |
| Caelo     | Hard fat in pastilles | 12158104            | 5       |
| Caelo     | Hard fat in pastilles | 13243411            | 4       |
| Caelo     | Hard fat in pastilles | 1909E-02328         | 1       |
| Bombastus | Hard fat in pastilles | 277212              | 2       |
| Caelo     | Wax, yellow           | 15023006            | 4       |
| Caelo     | Wax, yellow           | 15317608            | 6       |
| Caelo     | Wax, yellow           | 15317611            | 1       |
| Caelo     | Wax, yellow           | 15317613            | 5       |
| Caelo     | Wax, yellow           | 16038206            | 4       |
| Caelo     | Wax, yellow           | 16038203            | 4       |
| Caelo     | Cocoa butter          | 11117816            | 3       |
| Caelo     | Cocoa butter          | 11079612            | 2       |
| Caelo     | Cocoa butter          | 12040802            | 1       |
| Caelo     | Cocoa butter          | 12342003            | 8       |
| Bombastus | Wax, yellow           | 267702              | 2       |
| Klenk     | Wax, yellow           | 280A130115          | 15      |
| Klenk     | Wax, yellow           | 280A140306          | 8       |
| Klenk     | Wax, yellow           | 280A150528          | 4       |
| Klenk     | Wax, yellow           | 290A120627          | 5       |
| Caelo     | Wax, yellow           | 11017318            | 3       |
| Caelo     | Wax, yellow           | 12124810            | 7       |
| Caelo     | Wax, yellow           | 1214816             | 1       |
| Caelo     | Wax, yellow           | 12257009            | 9       |
| Caelo     | Wax, yellow           | 12367901            | 14      |
| Caelo     | Wax, yellow           | 12367904            | 4       |
| Caelo     | Wax, yellow           | 12367916            | 6       |
| Caelo     | Wax, yellow           | 12367916-3429311150 | 1       |
| Fagron    | Wax, yellow           | 12D23-N05           | 2       |
| Caelo     | Wax, yellow           | 13031206            | 8       |
| Caelo     | Wax, yellow           | 13335517            | 5       |
| Caelo     | Wax, yellow           | 14189912            | 3       |
| Caelo     | Wax, yellow           | 14336607            | 9       |
| Caelo     | Wax, yellow           | 1436607             | 1       |
| Caelo     | Wax, yellow           | 15292003            | 3       |
| Bombastus | Wax, yellow           | 279999              | 1       |
| Bombastus | Wax, yellow           | 285109              | 1       |
| Caelo     | Wax, yellow           | P146/14             | 1       |

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| <b>Supplier</b>      | <b>Substance</b>   | <b>Batch</b> | <b>Spectra</b> |
|----------------------|--------------------|--------------|----------------|
| Caelo                | Wax, bleached      | 14336620     | 1              |
| Caelo                | Wax, bleached      | 1529003      | 1              |
| Caelo                | Wax, bleached      | 15292009     | 2              |
| Caelo                | Cetyl palmitate 15 | 14351602     | 3              |
| Anzag                | Cetyl palmitate 15 | 12018208     | 1              |
| Gehe                 | Cetyl palmitate 15 | 8209646      | 1              |
| Caelo                | Cetyl palmitate 15 | 13131914     | 4              |
| Caelo                | Cetyl palmitate 15 | 13295919     | 14             |
| Caelo                | Cetyl palmitate 15 | 12331916     | 10             |
| Caelo                | Cetyl palmitate 15 | 13131911     | 2              |
| Caelo                | Cetyl palmitate 15 | 13295910     | 7              |
| Caelo                | Cetyl palmitate 15 | 11021502     | 1              |
| Caesar/Noweda        | Cetyl palmitate 15 | 13295909     | 1              |
| Caelo                | Cetyl palmitate 15 | 13131906     | 11             |
| Phönix               | Cetyl palmitate 15 | 13295919     | 1              |
| Caelo                | Cetyl palmitate 15 | 13295921     | 1              |
| Caelo                | Cetyl palmitate 15 | 14041505     | 1              |
| Caelo                | Cetyl palmitate 15 | 14060705     | 6              |
| Phoenix              | Cetyl palmitate 15 | 14060705     | 1              |
| Caelo                | Cetyl palmitate 15 | 14060706     | 8              |
| Caelo                | Cetyl palmitate 15 | 14060709     | 6              |
| Caelo                | Cetyl palmitate 15 | 14213705     | 3              |
| Caelo                | Cetyl palmitate 15 | 14213706     | 1              |
| Caelo                | Cetyl palmitate 15 | 14213709     | 1              |
| Apotärze             | Cetyl palmitate 15 | 1421371      | 1              |
| Caesar u Loretz      | Cetyl palmitate 15 | 14213710     | 1              |
| Caelo                | Cetyl palmitate 15 | 14213710     | 2              |
| Caelo                | Cetyl palmitate 15 | 14351601     | 2              |
| Caelo                | Cetyl palmitate 15 | 14351606     | 2              |
| Caelo                | Cetyl palmitate 15 | 14351607     | 1              |
| Caelo                | Cetyl palmitate 15 | 14351609     | 3              |
| Caelo                | Cetyl palmitate 15 | 14351612     | 11             |
| Fargon/Alliance HC   | Cetyl palmitate 15 | 14351612     | 1              |
| coelo/Sana           | Cetyl palmitate 15 | 14351612     | 1              |
| Caelo                | Cetyl palmitate 15 | 14351614     | 1              |
| Caelo                | Cetyl palmitate 15 | 15137202     | 1              |
| Caelo                | Cetyl palmitate 15 | 15301701     | 5              |
| Caesar/Noweda        | Cetyl palmitate 15 | 15301701     | 1              |
| Caelo                | Cetyl palmitate 15 | 15301703     | 7              |
| Caelo                | Cetyl palmitate 15 | 15301704     | 3              |
| Caelo                | Cetyl palmitate 15 | 15301705     | 4              |
| Caelo                | Cetyl palmitate 15 | 15301709     | 3              |
| Alliance H.          | Cetyl palmitate 15 | 15301709     | 1              |
| Caelo                | Cetyl palmitate 15 | 15301711     | 3              |
| Fischer/Phönix       | Cetyl palmitate 15 | 15301711     | 1              |
| Caelo                | Cetyl palmitate 15 | 15632        | 1              |
| Caelo                | Cetyl palmitate 15 | 16053803     | 7              |
| Caelo                | Cetyl palmitate 15 | 16053804     | 1              |
| Caelo                | Cetyl palmitate 15 | 16053805     | 2              |
| Caelo                | Cetyl palmitate 15 | 16053811     | 4              |
| Caelo                | Cetyl palmitate 15 | 16186805     | 6              |
| Sanacorp             | Cetyl palmitate 15 | 16186805     | 1              |
| Caelo                | Cetyl palmitate 15 | 16186806     | 1              |
| Caelo                | Cetyl palmitate 15 | 16186809     | 1              |
| Sanacorp             | Cetyl palmitate 15 | 8/AKD13      | 1              |
| sanacorp             | Cetyl palmitate 15 | 8/AKD14      | 1              |
| Caelo                | Cetyl palmitate 15 | 8/AKD16      | 1              |
| Caelo                | Cetyl palmitate 15 |              | 1              |
| Caesar & Loretz GmbH | Cetyl palmitate 15 | 10068402     | 2              |
| Caelo                | Cetyl palmitate 15 | 10068410     | 1              |

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| Supplier            | Substance             | Batch               | Spectra |
|---------------------|-----------------------|---------------------|---------|
| Caelo               | Cetyl palmitate 15    | 11042019            | 2       |
| Gehe                | Cetyl palmitate 15    | 11216007            | 1       |
| Caelo               | Cetyl palmitate 15    | 12018204            | 4       |
| Caelo               | Cetyl palmitate 15    | 12018204/Int212191  | 1       |
| Caelo               | Cetyl palmitate 15    | 12018204c           | 1       |
| Caelo               | Cetyl palmitate 15    | 12018208            | 10      |
| Caelo               | Cetyl palmitate 15    | 12018215            | 1       |
| Caelo               | Cetyl palmitate 15    | 12082901            | 1       |
| Caesar/Noweda       | Cetyl palmitate 15    | 12124811            | 3       |
| Caelo               | Cetyl palmitate 15    | 122228801/Int212191 | 1       |
| Caesar/Noweda       | Cetyl palmitate 15    | 122228801           | 1       |
| Caelo               | Cetyl palmitate 15    | 122228805           | 1       |
| Caelo               | Cetyl palmitate 15    | 122228808           | 4       |
| Euro OTC            | Cetyl palmitate 15    | 122228808           | 1       |
| Kehr                | Cetyl palmitate 15    | 122228818           | 1       |
| Caelo               | Cetyl palmitate 15    | 122228818           | 4       |
| Caelo               | Cetyl palmitate 15    | 12228808            | 1       |
| Phönix Gotha        | Cetyl palmitate 15    | 12331916            | 1       |
| Phönix, 04.09.13    | Cetyl palmitate 15    | 12331916            | 1       |
| Caelo               | Cetyl palmitate 15    | 12331919            | 2       |
| Fagron              | Cetyl palmitate 15    | 12C27-N07           | 2       |
| Fagron              | Cetyl palmitate 15    | 12D19-N02           | 1       |
| Caelo               | Cetyl palmitate 15    | 12D19-No2           | 1       |
| Fagron              | Cetyl palmitate 15    | 12D19-N02           | 1       |
| Caelo               | Cetyl palmitate 15    | 1313190             | 1       |
| Caelo               | Cetyl palmitate 15    | 13131905            | 2       |
| Alliance Healthcare | Cetyl palmitate 15    | 13131905            | 1       |
| Phönix              | Cetyl palmitate 15    | 13131906            | 1       |
| gehe                | Cetyl palmitate 15    | 13295919            | 1       |
| gepepharm/Kehr      | Cetyl palmitate 15    | 13295919            | 1       |
| Caelo               | Cetyl palmitate 15    | 26071201            | 1       |
| Caelo               | Cetyl palmitate 15    | 30101301            | 1       |
| Nachprüfung         | Cetyl palmitate 15    | 3012U01241          | 1       |
| Sanacorp            | Cetyl palmitate 15    | 8/AKD12             | 1       |
| Caelo               | Hard fat in pastilles | 12158119            | 1       |
| Fagron              | Hard fat in pastilles | 13243301            | 1       |
| Fagron              | Hard fat in pastilles | 12G04-N18           | 1       |
| Caelo               | Hard fat in pastilles | 13243401            | 1       |
| Caelo               | Hard fat in pastilles | 13243403            | 7       |
| Caelo               | Hard fat in pastilles | 13243409            | 3       |
| Caelo               | Hard fat in pastilles | 13243412            | 2       |
| Caelo               | Hard fat in pastilles | 13243418            | 4       |
| Caelo               | Hard fat in pastilles | 13243419            | 3       |
| Caelo               | Hard fat in pastilles | 13243420            | 1       |
| Caelo               | Hard fat in pastilles | 1412602             | 1       |
| Caelo               | Hard fat in pastilles | 14126202            | 5       |
| Caesar/Noweda       | Hard fat in pastilles | 14126203            | 1       |
| Caelo               | Hard fat in pastilles | 14126204            | 2       |
| Caelo               | Hard fat in pastilles | 14126205            | 1       |
| Caelo               | Hard fat in pastilles | 14126209            | 2       |
| Caelo               | Hard fat in pastilles | 14126210            | 3       |
| Caelo               | Hard fat in pastilles | 14126216            | 3       |
| Caelo               | Hard fat in pastilles | 14126217            | 3       |
| Caelo               | Hard fat in pastilles | 14126218            | 2       |
| Caelo               | Hard fat in pastilles | 14338703            | 2       |
| Caelo               | Hard fat in pastilles | 14338704            | 2       |
| Caelo               | Hard fat in pastilles | 14338706            | 1       |
| Caelo               | Hard fat in pastilles | 14338705            | 1       |
| Caelo               | Hard fat in pastilles | 14338707            | 3       |
| Caelo               | Hard fat in pastilles | 14338708            | 2       |

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| <b>Supplier</b>            | <b>Substance</b>      | <b>Batch</b>     | <b>Spectra</b> |
|----------------------------|-----------------------|------------------|----------------|
| Caelo                      | Hard fat in pastilles | 14338711         | 2              |
| Fagron                     | Hard fat in pastilles | 14G03-B03-296731 | 1              |
| Fagron                     | Hard fat in pastilles | 14L01-B06-303380 | 3              |
| Caelo                      | Hard fat in pastilles | 15111402         | 1              |
| Caelo                      | Hard fat in pastilles | 15185002         | 16             |
| Cae4lo                     | Hard fat in pastilles | 15185002         | 1              |
| Rondell Apotheke           | Hard fat in pastilles | 15185002         | 1              |
| Caelo                      | Hard fat in pastilles | 15185003         | 7              |
| Caelo                      | Hard fat in pastilles | 15185005         | 11             |
| Euro OTC                   | Hard fat in pastilles | 15185005         | 1              |
| Caelo                      | Hard fat in pastilles | 15185007         | 1              |
| Caelo                      | Hard fat in pastilles | 15185009         | 3              |
| Caelo                      | Hard fat in pastilles | 1518505          | 1              |
| Fagron                     | Hard fat in pastilles | 15F03-B06        | 4              |
| Fagron                     | Hard fat in pastilles | 15F03-B06-308708 | 3              |
| Caelo                      | Hard fat in pastilles | 16021503         | 1              |
| Caelo                      | Hard fat in pastilles | 16274203         | 1              |
| Caelo                      | Hard fat in pastilles | 17041401         | 1              |
| Bombastus                  | Hard fat in pastilles | 287287           | 1              |
| Bombastus                  | Hard fat in pastilles | 293848           | 6              |
| Bombastus                  | Hard fat in pastilles | 302709           | 1              |
| Bombastus                  | Hard fat in pastilles | 306363           | 2              |
| Bombastus                  | Hard fat in pastilles | 263489           | 1              |
| Caelo                      | Hard fat in pastilles | 11109617         | 1              |
| Caelo                      | Hard fat in pastilles | 11109623         | 3              |
| Caelo                      | Hard fat in pastilles | 11285001         | 2              |
| sanacorp                   | Hard fat in pastilles | 267773           | 1              |
| Caelo                      | Hard fat in pastilles | 7101304          | 1              |
| Caelo                      | Hard fat in pastilles | 10158813         | 1              |
| Purren Apotheke            | Hard fat in pastilles | 10I03-N08        | 1              |
| Caesar&Loretz GmbH D-40... | Hard fat in pastilles | 11109617         | 1              |
| Caelo                      | Hard fat in pastilles | 11345904         | 1              |
| Noweda                     | Hard fat in pastilles | 11345909         | 1              |
| Caelo                      | Hard fat in pastilles | 11345909         | 2              |
| Caelo                      | Hard fat in pastilles | 11345917         | 5              |
| Caelo                      | Hard fat in pastilles | 11345918         | 8              |
| phönix, 19.12.2012         | Hard fat in pastilles | 11345918         | 1              |
| Anzag 17.01.2013           | Hard fat in pastilles | 11345918         | 1              |
| Caesar & Loretz GmbH, 4... | Hard fat in pastilles | 11345918         | 1              |
| Gehe                       | Hard fat in pastilles | 11345918         | 1              |
| Caelo                      | Hard fat in pastilles | 1135917          | 2              |
| Caelo                      | Hard fat in pastilles | 12111204         | 1              |
| Caesar & Loretz GmbH D-... | Hard fat in pastilles | 12158104         | 1              |
| Caelo                      | Hard fat in pastilles | 12158109         | 3              |
| Caelo                      | Hard fat in pastilles | 12158114         | 4              |
| Caelo                      | Hard fat in pastilles | 12158115         | 7              |
| Fagron                     | Hard fat in pastilles | 12158115         | 2              |
| Caelo                      | Hard fat in pastilles | 12158122         | 3              |
| Fagron                     | Hard fat in pastilles | 12K01-N12        | 2              |
| Gehe                       | Hard fat in pastilles | 13243403         | 1              |
| Caesar & Loretz GmbH, 4... | Hard fat in pastilles | 13243403         | 1              |
| Caelo                      | Hard fat in pastilles | 13243414         | 1              |
| Fagron                     | Hard fat in pastilles | 13D10-N06        | 1              |
| Sanacorp                   | Hard fat in pastilles | 14126203         | 1              |
| Caelo                      | Hard fat in pastilles | 2511A-02328      | 1              |
| Caelo                      | Hard fat in pastilles | 24011302         | 1              |
| Bombastus                  | Hard fat in pastilles | 273759           | 1              |
| China Medica               | Hard fat in pastilles | 3244303          | 1              |
| Phönix                     | Hard fat in pastilles | 277212           | 1              |
| Fargon                     | Hard fat in pastilles | 41319264         | 1              |

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| <b>Supplier</b>          | <b>Substance</b>      | <b>Batch</b>     | <b>Spectra</b> |
|--------------------------|-----------------------|------------------|----------------|
| Bombastus                | Hard fat in pastilles | 60084402         | 1              |
| Caelo                    | Hard fat in pastilles | 90915429         | 1              |
| Caelo                    | Hard fat in pastilles |                  | 1              |
| Fagron                   | Hard fat W35          | 15J08-B04        | 1              |
| Fagron                   | Hard fat W35          | 15J08-B04-322726 | 1              |
| Noweda                   | Hard fat W35          | 16027801         | 1              |
| Fagron                   | Hard fat W35          | 3914E-02328      | 1              |
| Caelo                    | Paraffin, hard        | 10194101         | 2              |
| Unisan                   | Paraffin, hard        | 11166911         | 1              |
| Caelo                    | Paraffin, hard        | 123654           | 1              |
| Caelo                    | Paraffin, hard        | 13109213         | 5              |
| Caelo                    | Paraffin, hard        | 13109214         | 6              |
| Caelo                    | Paraffin, hard        | 13109224         | 5              |
| Euro OTC                 | Paraffin, hard        | 13109224         | 1              |
| Caelo                    | Paraffin, hard        | 13390406         | 4              |
| Caelo                    | Paraffin, hard        | 13390408         | 1              |
| Caelo                    | Paraffin, hard        | 13390413         | 1              |
| Caelo                    | Paraffin, hard        | 13390415         | 2              |
| Phoenix goettingen 09.05 | Paraffin, hard        | 13390415         | 1              |
| Caelo                    | Paraffin, hard        | 14126202         | 1              |
| Caelo                    | Paraffin, hard        | 14286504         | 1              |
| Caelo                    | Paraffin, hard        | 14286511         | 2              |
| Caelo                    | Paraffin, hard        | 14286517         | 3              |
| Fagron                   | Paraffin, hard        | 14L01-B06        | 2              |
| Caelo                    | Paraffin, hard        | 1523002          | 1              |
| Caelo                    | Paraffin, hard        | 152320004        | 1              |
| Caelo                    | Paraffin, hard        | 15232004         | 3              |
| Caelo                    | Paraffin, hard        | 15295405         | 4              |
| Caelo                    | Paraffin, hard        | 15295406         | 1              |
| GEHE                     | Paraffin, hard        | 15295409         | 1              |
| Phoenix                  | Paraffin, hard        | 15295410         | 1              |
| Gehe                     | Paraffin, hard        | 15295410         | 1              |
| Cealo/AHD                | Paraffin, hard        | 15295411         | 2              |
| Caelo                    | Paraffin, hard        | 15295414         | 4              |
| Caelo                    | Paraffin, hard        | 16000903         | 2              |
| Caelo                    | Paraffin, hard        | 16000911         | 1              |
| Caelo                    | Paraffin, hard        | 16000912         | 1              |
| Caelo                    | Paraffin, hard        | 10194106         | 1              |
| Caelo                    | Paraffin, hard        | 11021202         | 1              |
| Caelo                    | Paraffin, hard        | 11166911         | 1              |
| Kehr                     | Paraffin, hard        | 11166916         | 1              |
| Caelo                    | Paraffin, hard        | 11363205         | 1              |
| Noweda                   | Paraffin, hard        | 11363206         | 1              |
| Caelo                    | Paraffin, hard        | 11363206         | 1              |
| Caelo                    | Paraffin, hard        | 11363220         | 3              |
| Caelo                    | Paraffin, hard        | 12252205         | 2              |
| Caelo                    | Paraffin, hard        | 12252206         | 1              |
| Caelo                    | Paraffin, hard        | 12252211         | 5              |
| Caelo                    | Paraffin, hard        | 12252221         | 2              |
| Caelo                    | Paraffin, hard        | 13109203         | 3              |
| Caelo                    | Paraffin, hard        | 13109221         | 1              |
| Caelo                    | Cocoa butter          | 13140404         | 23             |
| Caelo                    | Cocoa butter          | 13140405         | 4              |
| Caelo                    | Cocoa butter          | 13140407         | 21             |
| Euro OTC                 | Cocoa butter          | 13140409         | 1              |
| Caelo                    | Cocoa butter          | 13140409         | 1              |
| Caelo                    | Cocoa butter          | 13292001         | 2              |
| Caelo                    | Cocoa butter          | 13292006         | 4              |
| Caelo                    | Cocoa butter          | 13292007         | 11             |
| Caelo                    | Cocoa butter          | 13292011         | 2              |

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| <b>Supplier</b> | <b>Substance</b>           | <b>Batch</b> | <b>Spectra</b> |
|-----------------|----------------------------|--------------|----------------|
| Caelo           | Cocoa butter               | 13292012     | 3              |
| Caelo           | Cocoa butter               | 13292013     | 9              |
| Caelo           | Cocoa butter               | 14045104     | 21             |
| Caelo           | Cocoa butter               | 14123609     | 1              |
| Caelo           | Cocoa butter               | 14123611     | 5              |
| Caelo           | Cocoa butter               | 14123617     | 4              |
| Caelo           | Cocoa butter               | 14123620     | 4              |
| Caelo           | Cocoa butter               | 14123621     | 1              |
| Caelo           | Cocoa butter               | 14348906     | 6              |
| AHD             | Cocoa butter               | 14348906     | 1              |
| Caelo           | Cocoa butter               | 14348908     | 2              |
| Caelo           | Cocoa butter               | 15088903     | 1              |
| Caelo           | Cocoa butter               | 15088904     | 1              |
| Caelo           | Cocoa butter               | 15246102     | 1              |
| Caelo           | Cocoa butter               | 16316503     | 2              |
| Caelo           | Cocoa butter               | 16316508     | 4              |
| Caelo           | Cocoa butter               |              | 1              |
| Sanacorp        | Cocoa butter               | AKD28        | 1              |
| Herbasinica     | Cocoa butter               |              | 2              |
| Caelo           | Cocoa butter               | 11034718     | 1              |
| Caelo           | Cocoa butter               | 11034719     | 1              |
| Euro OTC        | Cocoa butter               | 11079604     | 1              |
| Caelo           | Cocoa butter               | 11117806     | 2              |
| Caelo           | Cocoa butter               | 11117813     | 1              |
| Noweda          | Cocoa butter               | 11117813     | 2              |
| Caelo           | Cocoa butter               | 11117820     | 1              |
| Caelo           | Cocoa butter               | 12040803     | 2              |
| Caelo           | Cocoa butter               | 12040807     | 1              |
| Caelo           | Cocoa butter               | 12040810     | 1              |
| Caelo           | Cocoa butter               | 12270201     | 2              |
| Caelo           | Cocoa butter               | 12270202     | 26             |
| Caelo           | Cocoa butter               | 12270203     | 5              |
| Caelo           | Cocoa butter               | 12270205     | 5              |
| Caelo           | Cocoa butter               | 12270206     | 11             |
| Caelo           | Cocoa butter               | 12270209     | 1              |
| Caelo           | Cocoa butter               | 12270210     | 2              |
| Caelo           | Cocoa butter               | 12270212     | 10             |
| Anzag           | Cocoa butter               | 12342004     | 1              |
| Caelo           | Cocoa butter               | 12342004     | 1              |
| Caelo           | Cocoa butter               | 13027202     | 5              |
| Caelo           | Cocoa butter               | 13027204     | 4              |
| Caelo           | Cocoa butter               | 13027207     | 5              |
| Sanacorp        | Cocoa butter               | 13027207     | 1              |
| Caelo           | Cocoa butter               | 13027221     | 5              |
| gehe 26.08.13   | Cocoa butter               | 13027221     | 1              |
| Caelo           | Cocoa butter               | 13027224     | 5              |
| Caelo           | Cocoa butter               | 13027226     | 4              |
| Caelo           | Cocoa butter               | 13027227     | 3              |
| Caelo           | Cocoa butter               | 13140401     | 1              |
| Caelo           | Cocoa butter               | 13140402     | 1              |
| Caelo           | Cocoa butter               | 13140406     | 3              |
| Caelo / Noweda  | Cocoa butter               | 13292011     | 1              |
| Caelo           | Cocoa butter               | 1392013      | 1              |
| Spinnrad        | Cocoa butter               | 512300202    | 1              |
| Caelo           | Cocoa butter               | 71326048     | 2              |
| Sanacorp        | Cocoa butter               | AKD27        | 1              |
| Caelo           | Paraffin, microcrystalline | 13274303     | 6              |
| Caelo           | Paraffin, microcrystalline | 14307106     | 1              |
| Caelo           | Paraffin, microcrystalline | 52622395     | 1              |
| Gehe            | Sodium dodecyl sulfate     | 14127404     | 1              |

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| <b>Supplier</b>    | <b>Substance</b>           | <b>Batch</b> | <b>Spectra</b> |
|--------------------|----------------------------|--------------|----------------|
| Caelo              | Sodium dodecyl sulfate     | 12153010     | 3              |
| Caelo              | Sodium dodecyl sulfate     | 13411302     | 2              |
| Caelo              | Sodium dodecyl sulfate     | 14127411     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 13411304     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 13411305     | 3              |
| Caelo              | Sodium dodecyl sulfate     | 14127406     | 2              |
| Caelo              | Sodium dodecyl sulfate     | 14224206     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 14283904     | 3              |
| Caelo              | Sodium dodecyl sulfate     | 15095403     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 15095404     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 15119907     | 2              |
| Caelo              | Sodium dodecyl sulfate     | 15344503     | 2              |
| Caelo              | Sodium dodecyl sulfate     | 15344505     | 2              |
| Ichthyol/Phönix    | Sodium dodecyl sulfate     | 15344510     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 15344510     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 15344511     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 15344515     | 2              |
| Fagron             | Sodium dodecyl sulfate     | 16229205     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 16229206     | 4              |
| Caelo              | Sodium dodecyl sulfate     | 26031508     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 13014604     | 2              |
| Caelo              | Sodium dodecyl sulfate     | 13014606     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 13099006     | 3              |
| Caelo              | Sodium dodecyl sulfate     | 13099008     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 13099011     | 3              |
| Caelo              | Sodium dodecyl sulfate     | 16229217     | 1              |
| Intern Drogen      | Sodium dodecyl sulfate     | 216991080    | 1              |
| Sanacorp           | Sodium dodecyl sulfate     | 5/AKD1       | 1              |
| Sanacorp           | Sodium dodecyl sulfate     | 5/AKD6       | 1              |
| Caelo              | Sodium dodecyl sulfate     | 11220208     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 12153003     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 12153004     | 1              |
| Caelo              | Sodium dodecyl sulfate     | 12153019     | 1              |
| Caelo              | Cocoa butter               | 515A-03176   | 1              |
| Gutenberg-Apotheke | Cocoa butter               | 13292007     | 1              |
| Caelo              | Cocoa butter               | 13292015     | 1              |
| Caelo              | Cocoa butter               | 13292019     | 1              |
| Caelo              | Cocoa butter               | 14304703     | 1              |
| Caelo              | Cocoa butter               | 16049201     | 1              |
| Caelo              | Cocoa butter               | 16316501     | 2              |
| Caelo              | Cocoa butter               | 11079607     | 2              |
| Caesar & Lorenz    | Cocoa butter               | 13140404     | 1              |
| Caelo              | Paraffin, microcrystalline | 13274308     | 1              |
| Caelo              | Paraffin, microcrystalline | 15412801     | 1              |
| Caelo              | Paraffin, microcrystalline | 14307108     | 2              |
| Caelo              | Paraffin, microcrystalline | 3042012M1    | 1              |
| Caelo              | Paraffin, microcrystalline | 7111201      | 1              |
| Caelo              | Paraffin, microcrystalline | 7111202      | 1              |
| Caelo              | Paraffin, microcrystalline | 12065104     | 1              |
| Caelo              | Paraffin, microcrystalline | 12095101     | 1              |
| Caelo              | Paraffin, microcrystalline | 12266304     | 1              |
| Caelo              | Paraffin, microcrystalline | 12355001     | 1              |
| Caelo              | Paraffin, microcrystalline | 13274301     | 1              |
| Noweda             | Paraffin, microcrystalline | 12266304     | 1              |
| Phönix             | Paraffin, microcrystalline | 13274301     | 1              |
| Caelo              | Paraffin, microcrystalline | 30101202     | 1              |
| Caelo              | Paraffin, hard             | 14286503     | 1              |
| Caelo              | Paraffin, hard             | 15295410     | 1              |
| Caelo              | Paraffin, hard             | 1136206      | 1              |
| Caelo              | Hard fat in pastilles      | 20071501     | 1              |

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| <b>Supplier</b>            | <b>Substance</b>      | <b>Batch</b>   | <b>Spectra</b> |
|----------------------------|-----------------------|----------------|----------------|
| Caelo                      | Hard fat in pastilles | 10356001       | 1              |
| Fagron                     | Hard fat in pastilles | 12I04-N11      | 1              |
| Caelo                      | Hard fat in pastilles | 13243416       | 1              |
| Fagron                     | Hard fat in pastilles | 13F26-N02      | 1              |
| Phytocomm                  | Hard fat in pastilles | 209314         | 2              |
| Klenk                      | Wax, yellow           | 280A120627     | 2              |
| Alliance                   | Wax, yellow           | 280A130115     | 1              |
| Noweda                     | Wax, yellow           | 280A120627     | 2              |
| Klenk                      | Wax, yellow           | 280-A120627    | 1              |
| Alliance Health 14.04.2... | Wax, yellow           | 280A130115     | 1              |
| Klenk                      | Wax, yellow           | 280A13011A     | 1              |
| Klenk                      | Wax, yellow           | 282A120627     | 1              |
| Klenk                      | Wax, yellow           | 290A140903     | 3              |
| Klenk                      | Wax, yellow           | 282A140306     | 1              |
| Klenk                      | Wax, yellow           | 290A150716     | 1              |
| Klenk                      | Wax, yellow           | 290A081210     | 1              |
| Klenk                      | Wax, yellow           | 290A110803     | 1              |
| Alliance Healthcare        | Wax, yellow           | 290A120627     | 1              |
| Caelo                      | Wax, yellow           | 4031403        | 1              |
| Caelo                      | Wax, yellow           | 10121302       | 1              |
| Caelo                      | Wax, yellow           | 6111407        | 1              |
| Finze                      | Wax, yellow           | 10145002       | 1              |
| Caelo                      | Wax, yellow           | 10364810       | 1              |
| Caelo                      | Wax, yellow           | 10145019       | 1              |
| Caelo                      | Wax, yellow           | 10364814       | 1              |
| Caelo                      | Wax, yellow           | 10364829       | 1              |
| Caelo                      | Wax, yellow           | 10364837       | 1              |
| Kehr                       | Wax, yellow           | 10F03-N09      | 1              |
| Caelo                      | Wax, yellow           | 110124         | 1              |
| Caelo                      | Wax, yellow           | 11017314       | 1              |
| Caelo                      | Wax, yellow           | 11017315       | 1              |
| Caelo                      | Wax, yellow           | 11101207       | 1              |
| Caelo                      | Wax, yellow           | 11285010       | 1              |
| Caelo                      | Wax, yellow           | 11285008       | 1              |
| Caesar & Loretz GmbH, 4... | Wax, yellow           | 11285008       | 1              |
| Caelo                      | Wax, yellow           | 11285014       | 2              |
| Caelo                      | Wax, yellow           | 11285015       | 1              |
| Noweda                     | Wax, yellow           | 11308305       | 1              |
| Caelo                      | Wax, yellow           | 11308305       | 1              |
| Caelo                      | Wax, yellow           | 11308311       | 2              |
| Caelo                      | Wax, yellow           | 12/AKD7        | 1              |
| Euro OTC                   | Wax, yellow           | 1201012-01     | 1              |
| Sanacorp                   | Wax, yellow           |                | 2              |
| Caelo                      | Wax, yellow           | 12041303       | 1              |
| Gehe                       | Wax, yellow           | 12079412       | 1              |
| Caelo                      | Wax, yellow           | 12091404       | 1              |
| Caelo                      | Wax, yellow           | 12124801       | 7              |
| Noweda                     | Wax, yellow           | 12124801       | 1              |
| Caelo                      | Wax, yellow           | 12124802       | 2              |
| Caelo                      | Wax, yellow           | 121248024-2015 | 1              |
| Caelo                      | Wax, yellow           | 12124805       | 6              |
| Großhandel                 | Wax, yellow           | 12124805       | 2              |
| Caelo                      | Wax, yellow           | 12124806       | 1              |
| Caelo                      | Wax, yellow           | 12124807       | 3              |
| Caelo                      | Wax, yellow           | 12124811       | 1              |
| Caelo                      | Wax, yellow           | 12124812       | 8              |
| Caelo                      | Wax, yellow           | 12124814       | 2              |
| Caelo                      | Wax, yellow           | 12124816       | 1              |
| Caelo                      | Wax, yellow           | 12124817       | 3              |
| Caelo                      | Wax, yellow           | 12257002       | 3              |

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| <b>Supplier</b>            | <b>Substance</b> | <b>Batch</b>   | <b>Spectra</b> |
|----------------------------|------------------|----------------|----------------|
| Caelo                      | Wax, yellow      | 1214812        | 1              |
| Caelo                      | Wax, yellow      | 12257004       | 2              |
| Sanacorp                   | Wax, yellow      | 12257009       | 1              |
| Caelo                      | Wax, yellow      | 12257012       | 4              |
| Hirsch                     | Wax, yellow      | 12257012       | 1              |
| Caelo                      | Wax, yellow      | 12257022       | 3              |
| Caelo                      | Wax, yellow      | 12330116       | 1              |
| Phönix                     | Wax, yellow      | 12367901       | 1              |
| Caesar & Loretz GmbH, 4... | Wax, yellow      | 12367901       | 1              |
| Phönix                     | Wax, yellow      | 12367904       | 1              |
| gehe 16.08.13              | Wax, yellow      | 12367904       | 1              |
| Caelo                      | Wax, yellow      | 12367910       | 8              |
| AHD , 04.09.13             | Wax, yellow      | 12367910       | 1              |
| Caesar & Loretz GmbH, 4... | Wax, yellow      | 12367910       | 1              |
| Gehe                       | Wax, yellow      | 12367910       | 1              |
| Sanacorp                   | Wax, yellow      | 12367910       | 1              |
| Caesar & Loretz GmbH       | Wax, yellow      | 12367910       | 1              |
| Caelo                      | Wax, yellow      | 12367911       | 2              |
| Caelo                      | Wax, yellow      | 12367912       | 5              |
| Caelo                      | Wax, yellow      | 12367915       | 10             |
| AHD,18.10.13               | Wax, yellow      | 12367915       | 1              |
| Phönix                     | Wax, yellow      | 12367915       | 1              |
| Caelo                      | Wax, yellow      | 12367921       | 1              |
| Fagron                     | Wax, yellow      | 12K20B05287421 | 1              |
| PHOENIX 24.07.2014         | Wax, yellow      | 13001206       | 1              |
| Caelo                      | Wax, yellow      | 13031201       | 6              |
| Phönix                     | Wax, yellow      | 13031206       | 1              |
| Caelo                      | Wax, yellow      | 13031220       | 3              |
| Caesar/Noweda              | Wax, yellow      | 13031220       | 1              |
| Caelo                      | Wax, yellow      | 13031221       | 1              |
| Caelo                      | Wax, yellow      | 13031222       | 4              |
| Caelo                      | Wax, yellow      | 13031231       | 8              |
| Ichthyol                   | Wax, yellow      | 13031239       | 1              |
| Caelo                      | Wax, yellow      | 13031239       | 10             |
| Caelo                      | Wax, yellow      | 13031240       | 1              |
| Caelo                      | Wax, yellow      | 13051401       | 1              |
| Caelo                      | Wax, yellow      | 13335502       | 9              |
| Caelo                      | Wax, yellow      | 13061503       | 1              |
| Großhandel                 | Wax, yellow      | 13335502       | 1              |
| Sanacorp                   | Wax, yellow      | 13335502       | 1              |
| Cealo/Gehe                 | Wax, yellow      | 13335502       | 1              |
| GEHE                       | Wax, yellow      | 13335502       | 1              |
| Caelo                      | Wax, yellow      | 13335503       | 7              |
| Caelo                      | Wax, yellow      | 13335505       | 1              |
| Caelo                      | Wax, yellow      | 13335507       | 4              |
| Caelo                      | Wax, yellow      | 13335508       | 1              |
| Caelo                      | Wax, yellow      | 13335509       | 4              |
| Klenk                      | Wax, yellow      | 13335513       | 1              |
| Caelo                      | Wax, yellow      | 13335513       | 3              |
| Caelo                      | Wax, yellow      | 13335516       | 4              |
| Caelo                      | Wax, yellow      | 13335518       | 1              |
| Caelo                      | Wax, yellow      | 1335503        | 1              |
| Caelo                      | Wax, yellow      | 13378603       | 1              |
| Sanacorp                   | Wax, yellow      | 13378619       | 1              |
| Caelo                      | Wax, yellow      | 13378619       | 16             |
| Caelo                      | Wax, yellow      | 13378630       | 2              |
| Caelo                      | Wax, yellow      | 13378634       | 7              |
| Caelo                      | Wax, yellow      | 13378636       | 1              |
| Caelo                      | Wax, yellow      | 13378639       | 3              |
| Caelo                      | Wax, yellow      | 13378640       | 2              |

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| <b>Supplier</b>          | <b>Substance</b> | <b>Batch</b>     | <b>Spectra</b> |
|--------------------------|------------------|------------------|----------------|
| Fagron                   | Wax, yellow      | 13804-N04        | 1              |
| Fagron                   | Wax, yellow      | 13B04-N04        | 2              |
| Fagron                   | Wax, yellow      | 13102-B01        | 1              |
| Fagron                   | Wax, yellow      | 13L02-B01-291452 | 1              |
| Fagron                   | Wax, yellow      | 13L02-B01-294113 | 1              |
| Fagron                   | Wax, yellow      | 13L02-B01-294114 | 1              |
| Euroo                    | Wax, yellow      | 1407013-01       | 1              |
| Euro OTC                 | Wax, yellow      | 1407013-01       | 1              |
| Caelo                    | Wax, yellow      | 1418915          | 1              |
| Caelo                    | Wax, yellow      | 14189901         | 2              |
| Caelo                    | Wax, yellow      | 14189902         | 2              |
| Caelo                    | Wax, yellow      | 14189906         | 1              |
| Caelo                    | Wax, yellow      | 14189907         | 3              |
| Caelo                    | Wax, yellow      | 14189908         | 1              |
| Caelo                    | Wax, yellow      | 14189909         | 5              |
| Caelo                    | Wax, yellow      | 14189913         | 3              |
| Caelo                    | Wax, yellow      | 14189914         | 4              |
| Caelo                    | Wax, yellow      | 14189917         | 1              |
| Caelo                    | Wax, yellow      | 14189919         | 1              |
| Fagron                   | Wax, yellow      | 14189920         | 1              |
| Caelo                    | Wax, yellow      | 14336605         | 2              |
| Caelo                    | Wax, yellow      | 14336608         | 3              |
| Caelo                    | Wax, yellow      | 14336609         | 2              |
| Caelo                    | Wax, yellow      | 14336616         | 6              |
| Fagron                   | Wax, yellow      | 14336616         | 1              |
| Caelo                    | Wax, yellow      | 14336618         | 1              |
| Caelo                    | Wax, yellow      | 14336620         | 3              |
| Caelo                    | Wax, yellow      | 1436616          | 1              |
| Caelo                    | Wax, yellow      | 1436620          | 1              |
| Caelo                    | Wax, yellow      | 14G07-B04-300495 | 1              |
| Fagron                   | Wax, yellow      | 14G07-B04-300495 | 2              |
| Caelo                    | Wax, yellow      | 15022902         | 4              |
| Caelo                    | Wax, yellow      | 15022903         | 1              |
| Caelo                    | Wax, yellow      | 15022904         | 2              |
| Caelo                    | Wax, yellow      | 15022907         | 1              |
| Caelo                    | Wax, yellow      | 15022908         | 5              |
| Noweda                   | Wax, yellow      | 15023002         | 1              |
| Caelo                    | Wax, yellow      | 15023003         | 3              |
| Caelo                    | Wax, yellow      | 15023004         | 6              |
| Caelo                    | Wax, yellow      | 15041301         | 1              |
| Phoenix goettingen 08.05 | Wax, yellow      | 15098901         | 1              |
| Caelo                    | Wax, yellow      | 15098902         | 2              |
| Caelo                    | Wax, yellow      | 152920004        | 1              |
| Caelo                    | Wax, yellow      | 15292004         | 9              |
| Caelo                    | Wax, yellow      | 15292005         | 3              |
| Caelo                    | Wax, yellow      | 15292007         | 1              |
| Caelo                    | Wax, yellow      | 15292009         | 1              |
| Caelo                    | Wax, yellow      | 15292014         | 2              |
| Caelo                    | Wax, yellow      | 15292022         | 1              |
| Caelo                    | Wax, yellow      | 15317602         | 4              |
| Caelo                    | Wax, yellow      | 15317601         | 2              |
| Caelo                    | Wax, yellow      | 15317603         | 3              |
| Caelo                    | Wax, yellow      | 15317604         | 1              |
| Caelo                    | Wax, yellow      | 15317607         | 3              |
| Caelo                    | Wax, yellow      | 16038201         | 5              |
| Caelo                    | Wax, yellow      | 17011403         | 1              |
| Caelo                    | Wax, yellow      | 17041402         | 1              |
| Caelo                    | Wax, yellow      | 17121202         | 1              |
| Caelo                    | Wax, yellow      | 20031516         | 1              |
| Caelo                    | Wax, yellow      | 18121201         | 1              |

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| Supplier        | Substance     | Batch            | Spectra |
|-----------------|---------------|------------------|---------|
| Caelo           | Wax, yellow   | 17121201         | 1       |
| Caelo           | Wax, yellow   | 20031517         | 1       |
| Caelo           | Wax, yellow   | 20071503         | 1       |
| Caelo           | Wax, yellow   | 22071301         | 1       |
| Caelo           | Wax, yellow   | 2179             | 1       |
| Bombastus       | Wax, yellow   | 270682           | 3       |
| Caelo           | Wax, yellow   | 26091302         | 1       |
| Caelo           | Wax, yellow   | 28011501         | 1       |
| Caelo           | Wax, yellow   | 30011407         | 1       |
| Caelo           | Wax, yellow   | 30101308         | 1       |
| Caelo           | Wax, yellow   | 4910A-01239      | 1       |
| Klenk           | Wax, bleached | 280A150528       | 5       |
| Klenk           | Wax, bleached | 280A160311       | 3       |
| Caelo           | Wax, bleached | 280A150528       | 1       |
| Klenk           | Wax, bleached | 290A150716       | 1       |
| Caelo           | Wax, bleached | 1/AKD13          | 1       |
| Caelo           | Wax, bleached | 14336621         | 1       |
| Caelo           | Wax, bleached | 15292002         | 1       |
| Caelo           | Wax, bleached | 15292003         | 5       |
| Phoenix         | Wax, bleached | 15292003         | 1       |
| Caelo           | Wax, bleached | 15292005         | 2       |
| Caelo           | Wax, bleached | 15292004         | 1       |
| Caelo           | Wax, bleached | 15292010         | 1       |
| Caelo           | Wax, bleached | 15292011         | 1       |
| Caelo           | Wax, bleached | 15292014         | 7       |
| Caelo           | Wax, bleached | 16163101         | 2       |
| Caelo           | Wax, bleached | 15292022         | 1       |
| Caelo           | Wax, bleached | 16163105         | 6       |
| Caelo           | Wax, bleached | 16163109         | 3       |
| Caelo           | Wax, bleached | 16163114         | 1       |
| Fagron          | Wax, bleached | 16A28-B10-322948 | 1       |
| Fagron          | Wax, bleached | 2155             | 1       |
| Caelo           | Wax, yellow   | 14189915         | 1       |
| Caelo           | Wax, yellow   | 15098901         | 1       |
| cae             | Wax, yellow   | 15317608         | 1       |
| Phönix          | Wax, yellow   | 15317609         | 1       |
| Caelo           | Wax, yellow   | 15317609         | 7       |
| Caelo           | Wax, yellow   | 15317610         | 3       |
| Caesar & Loretz | Wax, yellow   | 15317613         | 1       |
| Caelo           | Wax, yellow   | 1595             | 1       |
| Caesar & Loretz | Wax, yellow   | 16038201         | 1       |
| Caelo           | Wax, yellow   | 16038202         | 5       |
| Caelo           | Wax, yellow   | 17011604         | 1       |

- 68 107 spectra from 414 *Apo-Ident* customers from a total of 23 284 batches from a further 688 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Waxes / Fats* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Waxes / Fats* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following

table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 1207          | 0              | 70 179        |
| <b>Type B</b> | 0              | 1330          | 83             | 145 316       |
| <b>Type C</b> | 0              | 1470          | 56             | 68 107        |

The substance/substance group *Waxes / Fats* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 99.5029 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 94.1260 % (> 93.9137 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | 96.3303 % (> 96.1337 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20747     | 22767               | 9.72                         | 36.79                           |
| 20865     | 20865               | 0.00                         | 36.26                           |
| 20986     | 20986               | 0.00                         | 37.37                           |
| 21067     | 22479               | 6.03                         | 43.97                           |
| 21433     | 22767               | 7.26                         | 33.46                           |
| 21482     | 23067               | 13.62                        | 56.23                           |
| 21483     | 21483               | 0.00                         | 30.37                           |
| 21682     | 21682               | 0.00                         | 36.29                           |
| 21731     | 22349               | 1.92                         | 39.74                           |
| 21766     | 22330               | 2.85                         | 36.29                           |
| 21875     | 21984               | 4.19                         | 34.38                           |
| 21880     | 21880               | 0.00                         | 44.32                           |
| 21984     | 21984               | 0.00                         | 35.93                           |
| 22244     | 22767               | 9.14                         | 36.64                           |
| 22245     | 22767               | 5.38                         | 33.41                           |
| 22325     | 21984               | 2.72                         | 34.47                           |
| 22330     | 22330               | 0.00                         | 37.12                           |
| 22338     | 21880               | 4.94                         | 44.87                           |
| 22348     | 23067               | 4.12                         | 57.49                           |
| 22349     | 22349               | 0.00                         | 39.92                           |
| 22352     | 23278               | 4.42                         | 37.06                           |
| 22479     | 22479               | 0.00                         | 43.74                           |

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| <b>Sample ID</b> | <b>Reference sample ID</b> | <b>Distance to reference sample</b> | <b>Distance to next foreign sample</b> |
|------------------|----------------------------|-------------------------------------|----------------------------------------|
| 22486            | 22486                      | 0.00                                | 32.48                                  |
| 22767            | 22767                      | 0.00                                | 31.14                                  |
| 22956            | 22767                      | 12.34                               | 34.74                                  |
| 23067            | 23067                      | 0.00                                | 57.85                                  |
| 23242            | 23278                      | 8.20                                | 37.87                                  |
| 23278            | 23278                      | 0.00                                | 35.33                                  |
| 23565            | 22479                      | 20.40                               | 45.72                                  |
| 23601            | 21880                      | 2.00                                | 43.04                                  |
| 23707            | 23067                      | 3.47                                | 59.52                                  |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Wool alcohols**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20495-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Wool alcohols; Alcoholes adipis lanae; Alcoholes lanae

### Special notes

When selecting the *Wool alcohols* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Wool alcohols*:

| Supplier | Substance     | Batch    | Sample ID | Spectra | Certificate |
|----------|---------------|----------|-----------|---------|-------------|
| Caelo    | Wool alcohols | 13380601 | 21520     | 40      | 1412037     |
| Caelo    | Wool alcohols | 153703   | 22328     | 40      | 20151111*   |
| Caelo    | Wool alcohols | 153703   | 22329     | 40      | 20151111*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Wool alcohols*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 120 spectra of 4 reference samples from the substance/substance group *Wool alcohols*.

| Supplier | Substance     | Batch    | Sample ID          | Spectra |
|----------|---------------|----------|--------------------|---------|
| Caelo    | Wool alcohols | 11214708 | 20495              | 40      |
| Caelo    | Wool alcohols | 153703   | 22328 <sup>†</sup> | 20      |
| Caelo    | Wool alcohols | 153703   | 22329 <sup>†</sup> | 20      |
| Caelo    | Wool alcohols | 163530   | 23098              | 40      |

- 146 609 spectra from a total of 3191 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 14 spectra from 10 *Apo-Ident* customers from 11 batches from the substance/substance group *Wool alcohols*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier      | Substance     | Batch    | Spectra |
|---------------|---------------|----------|---------|
| Caelo         | Wool alcohols | 13071502 | 1       |
| Caelo         | Wool alcohols | 13226408 | 1       |
| Caelo/ Noweda | Wool alcohols | 13380601 | 1       |
| Caelo         | Wool alcohols | 15304502 | 1       |
| Caelo         | Wool alcohols | 15304505 | 1       |
| Caelo         | Wool alcohols | 13380601 | 1       |
| Caelo         | Wool alcohols | 17169701 | 1       |
| Caelo         | Wool alcohols | 23101408 | 1       |
| Caelo         | Wool alcohols | 11011401 | 1       |
| Caelo         | Wool alcohols | 12340505 | 1       |
| Caelo         | Wool alcohols | 13083906 | 3       |
| Caelo         | Wool alcohols | 13083912 | 1       |

- 69 619 spectra from 414 *Apo-Ident* customers from a total of 23 790 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Wool alcohols* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Wool alcohols* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 120           | 0              | 146 609       |
| <b>Type C</b> | 0              | 14            | 0              | 69 619        |

The substance/substance group *Wool alcohols* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 95.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested

reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21520     | 21520               | 0.00                         | 53.01                           |
| 22328     | 22328               | 0.00                         | 38.33                           |
| 22329     | 22329               | 0.00                         | 38.66                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Xylitol**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20994-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Xylitol; Xylitolum

### Special notes

When selecting the *Xylitol* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Xylitol*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------|------------------|-----------|---------|--------------------|
| Fagron   | Xylitol   | 14G04-B04-298356 | 21754     | 40      | AR-15-FG-008046-01 |
| Caelo    | Xylitol   | 14068206         | 21755     | 40      | 20140317           |
| Caelo    | Xylitol   | 15135405         | 22248     | 40      | 20150417           |
| Fagron   | Xylitol   | 14G04-B04-303524 | 22254     | 40      | 20140919           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *Xylitol*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 320 spectra of 10 reference samples from the substance/substance group *Xylitol*.

| Supplier    | Substance | Batch            | Sample ID          | Spectra |
|-------------|-----------|------------------|--------------------|---------|
| Dr. Pfeifer | Xylitol   | pending          | 20633              | 40      |
| Dr. Pfeifer | Xylitol   | 10BIZU130702     | 20994              | 40      |
| Dr. Pfeifer | Xylitol   | 130610           | 21099              | 40      |
| Fagron      | Xylitol   | 14G04-B04-298356 | 21754 <sup>†</sup> | 20      |
| Caelo       | Xylitol   | 14068206         | 21755 <sup>†</sup> | 20      |
| Caelo       | Xylitol   | 15135405         | 22248 <sup>†</sup> | 20      |
| Fagron      | Xylitol   | 14G04-B04-303524 | 22254 <sup>†</sup> | 20      |
| Caelo       | Xylitol   | 15388101         | 22578              | 40      |
| Caelo       | Xylitol   | 15135405         | 22579              | 40      |
| Caelo       | Xylitol   | 163174           | 23061              | 40      |

- 146 409 spectra from a total of 3186 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 22 spectra from 12 *Apo-Ident* customers from 17 batches from the substance/substance group *Xylitol*.

| Supplier | Substance | Batch            | Spectra |
|----------|-----------|------------------|---------|
| Caelo    | Xylitol   | 12240612         | 1       |
| Caelo    | Xylitol   | 13230302         | 2       |
| Caelo    | Xylitol   | 13230305         | 1       |
| Fagron   | Xylitol   | 13H28N10         | 1       |
| Caelo    | Xylitol   | 13230315         | 1       |
| Fagron   | Xylitol   | 13H28-N10        | 2       |
| Caelo    | Xylitol   | 14061401         | 1       |
| Caelo    | Xylitol   | 14G04-B04-298356 | 2       |
| Fagron   | Xylitol   | 14G04-B04-303524 | 2       |
| Caelo    | Xylitol   | 5112I-02787      | 1       |
| Caelo    | Xylitol   | 12039003         | 1       |
| Fagron   | Xylitol   | 13/23-N06        | 1       |
| Caelo    | Xylitol   | 13230309         | 1       |
| Caelo    | Xylitol   | 15135401         | 1       |
| Caelo    | Xylitol   | 15388104         | 2       |
| Caelo    | Xylitol   | 16317401         | 1       |
| Caelo    | Xylitol   | 3314M-02787      | 1       |

- 69 611 spectra from 414 *Apo-Ident* customers from a total of 23 784 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Xylitol* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Xylitol* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 320           | 0              | 146 409       |
| <b>Type C</b> | 0              | 22            | 0              | 69 611        |

The substance/substance group *Xylitol* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 98.1250 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 72.7273 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21754     | 21754               | 0.00                         | 29.49                           |
| 21755     | 21754               | 6.59                         | 36.26                           |
| 22248     | 21754               | 7.00                         | 36.61                           |
| 22254     | 21754               | 1.95                         | 31.03                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Xylometazoline hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20025-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Xylometazoline hydrochloride; Xylometazolini hydrochloridum; Xylometazolinum hydrochloricum

### Special notes

When selecting the *Xylometazoline hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Xylometazoline hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate        |
|----------|---------------------|------------------|-----------|---------|--------------------|
| Caelo    | Xylometazoline h... | 13344901         | 21516     | 40      | 1501655            |
| Fagron   | Xylometazoline h... | 13I18-B03-295481 | 21722     | 40      | AR-15-FG-007785-01 |
| Fagron   | Xylometazoline h... | 14K19-B05-305006 | 21927     | 40      | 20141128           |
| Caelo    | Xylometazoline h... | 16074211         | 23246     | 40      | 20160318           |
| Fagron   | Xylometazoline h... | 14K19-B05-305006 | 21927SI   | 40      | 20141128           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Xylometazoline hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 440 spectra of 12 reference samples from the substance/substance group *Xylometazoline hydrochloride*.

| Supplier | Substance                    | Batch            | Sample ID            | Spectra |
|----------|------------------------------|------------------|----------------------|---------|
| Caelo    | Xylometazoline hydrochloride | 91206209         | 20025                | 40      |
| Caelo    | Xylometazoline hydrochloride | 13344901         | 21516 <sup>†</sup>   | 20      |
| Caelo    | Xylometazoline hydrochloride | 13344901         | 21517                | 60      |
| Fagron   | Xylometazoline hydrochloride | 13I18-B03-295481 | 21722 <sup>†</sup>   | 20      |
| Fagron   | Xylometazoline hydrochloride | 14K19-B05-305006 | 21927 <sup>†</sup>   | 20      |
| Caelo    | Xylometazoline hydrochloride | 170739           | 23314                | 40      |
| Caelo    | Xylometazoline hydrochloride | 170739           | 23320                | 40      |
| Caelo    | Xylometazoline hydrochloride | 13344901         | 21517SI              | 60      |
| Fagron   | Xylometazoline hydrochloride | 14K19-B05-305006 | 21927SI <sup>†</sup> | 20      |
| Caelo    | Xylometazoline hydrochloride | 16074211         | 23246SI              | 40      |
| Caelo    | Xylometazoline hydrochloride | 170739           | 23314SI              | 40      |
| Caelo    | Xylometazoline hydrochloride | 170739           | 23320SI              | 40      |

- 146 289 spectra from a total of 3188 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 94 spectra from 61 *Apo-Ident* customers from 36 batches from the substance/substance group *Xylometazoline hydrochloride*.

| Supplier  | Substance                    | Batch            | Spectra |
|-----------|------------------------------|------------------|---------|
| Caelo     | Xylometazoline hydrochloride | 10118821         | 3       |
| Caelo     | Xylometazoline hydrochloride | 12287203         | 10      |
| Caelo     | Xylometazoline hydrochloride | 2031502          | 1       |
| Caelo     | Xylometazoline hydrochloride | 12287212         | 2       |
| Caelo     | Xylometazoline hydrochloride | 13171202         | 11      |
| Celoa vdL | Xylometazoline hydrochloride | 13171202         | 1       |
| Caelo     | Xylometazoline hydrochloride | 13171205         | 2       |
| Fagron    | Xylometazoline hydrochloride | 1318-B03-295479  | 1       |
| Caelo     | Xylometazoline hydrochloride | 13344908         | 2       |
| Caelo     | Xylometazoline hydrochloride | 13344901         | 1       |
| Fagron    | Xylometazoline hydrochloride | 13I09-N02        | 1       |
| Sanacorp  | Xylometazoline hydrochloride | 15037906         | 1       |
| Caelo     | Xylometazoline hydrochloride | 15037906         | 1       |
| Anzag     | Xylometazoline hydrochloride | 15037907         | 2       |
| Caelo     | Xylometazoline hydrochloride | 15037907         | 2       |
| Caelo     | Xylometazoline hydrochloride | 15037910         | 3       |
| Caelo     | Xylometazoline hydrochloride | 15037912         | 2       |
| Caelo     | Xylometazoline hydrochloride | 15292803         | 4       |
| Caelo     | Xylometazoline hydrochloride | 15292804         | 8       |
| Caelo     | Xylometazoline hydrochloride | 160740209        | 1       |
| Caelo     | Xylometazoline hydrochloride | 16074201         | 2       |
| Caelo     | Xylometazoline hydrochloride | 16074205         | 1       |
| Fagron    | Xylometazoline hydrochloride | 15Jo6-B99-313751 | 1       |
| Caelo     | Xylometazoline hydrochloride | 9276404          | 1       |
| Caelo     | Xylometazoline hydrochloride | 9278404          | 1       |
| Gehe      | Xylometazoline hydrochloride | 10118802         | 1       |
| Sanacorp  | Xylometazoline hydrochloride | 12027902         | 1       |
| Noweda    | Xylometazoline hydrochloride | 12027902         | 1       |
| Caelo     | Xylometazoline hydrochloride | 10118805         | 1       |
| Caelo     | Xylometazoline hydrochloride | 12027906         | 4       |
| Anzag     | Xylometazoline hydrochloride | 12027911         | 1       |
| Caelo     | Xylometazoline hydrochloride | 1207906          | 1       |
| Caelo     | Xylometazoline hydrochloride | 12287201         | 2       |
| Noweda    | Xylometazoline hydrochloride | 12287203         | 1       |
| Caelo     | Xylometazoline hydrochloride | 12287204         | 2       |
| Caelo     | Xylometazoline hydrochloride | 12287210         | 7       |
| Fagron    | Xylometazoline hydrochloride | 12287210         | 1       |
| Caelo     | Xylometazoline hydrochloride | 12287213         | 1       |
| Fagron    | Xylometazoline hydrochloride | 12G31-N01        | 1       |
| Caelo     | Xylometazoline hydrochloride | 13171203         | 1       |
| Fagron    | Xylometazoline hydrochloride | 13E06-N11        | 1       |
| Fagron    | Xylometazoline hydrochloride | 13171203         | 1       |
| Caelo     | Xylometazoline hydrochloride | 24111202         | 1       |

- 69 539 spectra from 414 *Apo-Ident* customers from a total of 23 765 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).



## Validation results

The validation runs checked whether the substance/substance group *Xylometazoline hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Xylometazoline hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|        | False positive | True positive | False negative | True negative |
|--------|----------------|---------------|----------------|---------------|
| Type A | 0              | 200           | 0              | 71 186        |
| Type B | 0              | 422           | 18             | 146 289       |
| Type C | 0              | 91            | 3              | 69 539        |

The substance/substance group *Xylometazoline hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|        | Specificity              | Recognition rate         |
|--------|--------------------------|--------------------------|
| Type A | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| Type B | 100.0000 % (> 99.9923 %) | 95.9091 % (> 95.2273 %)  |
| Type C | 100.0000 % (> 99.8813 %) | 96.8085 % (> 93.6170 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21516     | 21516               | 0.00                         | 43.02                           |
| 21722     | 21722               | 0.00                         | 52.62                           |
| 21927     | 21722               | 5.96                         | 52.60                           |
| 23246     | 21722               | 8.43                         | 52.86                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Xylose**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20517-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Xylose; Xylosum

### Special notes

When selecting the *Xylose* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Xylose*:

| Supplier | Substance | Batch            | Sample ID | Spectra | Certificate        |
|----------|-----------|------------------|-----------|---------|--------------------|
| Caelo    | Xylose    | 14218902         | 21606     | 40      | AR-14-FG-013086-01 |
| Fagron   | Xylose    | 13A31-B40-292395 | 21763     | 40      | 20140407           |
| Caelo    | Xylose    | 17160902         | 23413     | 40      | 20170704           |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Xylose*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

### Type B Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 7 reference samples from the substance/substance group *Xylose*.

| Supplier | Substance | Batch            | Sample ID          | Spectra |
|----------|-----------|------------------|--------------------|---------|
| Fagron   | Xylose    | 11L09-N11        | 20517              | 40      |
| Caelo    | Xylose    | 13133402         | 20868              | 40      |
| Caelo    | Xylose    | 14218902         | 21606 <sup>†</sup> | 20      |
| Fagron   | Xylose    | 13A31-B40-292395 | 21763 <sup>†</sup> | 20      |
| Caelo    | Xylose    | 162064           | 22758              | 40      |
| Fagron   | Xylose    | 16A25-B05-328261 | 23524              | 40      |
| Caelo    | Xylose    | 171609           | 23656              | 40      |

- 146 489 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

### Type C Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 34 spectra from 11 *Apo-Ident* customers from 23 batches from the substance/substance group *Xylose*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier                | Substance | Batch            | Spectra |
|-------------------------|-----------|------------------|---------|
| Fagron                  | Xylose    | 5031510          | 1       |
| Caelo                   | Xylose    | 5031501          | 1       |
| Eigenherstellung        | Xylose    | 80414HJK01       | 1       |
| Fagron                  | Xylose    | 80414PJK01       | 1       |
| Fagron                  | Xylose    | 10121401         | 1       |
| Gehe                    | Xylose    | 1000110821       | 1       |
| Caelo                   | Xylose    | 11031501         | 1       |
| Caelo                   | Xylose    | 12120101         | 1       |
| Gehe                    | Xylose    | 11J06-N01        | 1       |
| Caelo                   | Xylose    | 12120102         | 3       |
| Caelo                   | Xylose    | 13133404         | 2       |
| Caelo                   | Xylose    | 13133414         | 3       |
| Caelo                   | Xylose    | 13133410         | 1       |
| Fagron                  | Xylose    | 13133415         | 1       |
| Phoenix 20.06.2014      | Xylose    | 13A31-B04-292396 | 1       |
| Phoenix Goettin         | Xylose    | 13133422         | 1       |
| Ebert & Jacobi 12.07... | Xylose    | 16002301         | 2       |
| Caelo                   | Xylose    | 16002302         | 2       |
| Fagron                  | Xylose    | 14E-B03300658    | 1       |
| Caelo                   | Xylose    | 14218903         | 1       |
| Fagron                  | Xylose    | 28111405         | 1       |
| Gehe                    | Xylose    | xrf12020201      | 5       |
| Falcento                | Xylose    | 2013051801       | 1       |

- 69 599 spectra from 414 *Apo-Ident* customers from a total of 23 778 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Xylose* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Xylose* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 240           | 0              | 146 489       |
| <b>Type C</b> | 0              | 34            | 0              | 69 599        |

The substance/substance group *Xylose* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 100.0000 % (> 82.3529 %) |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21606     | 21606               | 0.00                         | 60.06                           |
| 21763     | 21606               | 9.72                         | 59.67                           |
| 23413     | 21606               | 10.67                        | 59.57                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Zinc acetate dihydrate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20398-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Zinc acetate dihydrate; Zinci acetat dihydricus; Zincum aceticum purum

### Special notes

When selecting the *Zinc acetate dihydrate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Zinc acetate dihydrate*:

| Supplier | Substance             | Batch    | Sample ID | Spectra | Certificate |
|----------|-----------------------|----------|-----------|---------|-------------|
| Caelo    | Zinc acetate dihyd... | 15383301 | 22728     | 40      | 20151127    |
| Caelo    | Zinc acetate dihyd... | 153833   | 23030     | 40      | 20151127*   |
| Caelo    | Zinc acetate dihyd... | 170204   | 23031     | 40      | 20170126*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *Zinc acetate dihydrate*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 200 spectra of 5 reference samples from the substance/substance group *Zinc acetate dihydrate*.

| Supplier | Substance              | Batch    | Sample ID | Spectra |
|----------|------------------------|----------|-----------|---------|
| Caelo    | Zinc acetate dihydrate | 10302505 | 20398     | 40      |
| Caelo    | Zinc acetate dihydrate | 11354901 | 20492     | 40      |
| Caelo    | Zinc acetate dihydrate | 11354902 | 20504     | 40      |
| Caelo    | Zinc acetate dihydrate | 17020404 | 23514     | 40      |
| Caelo    | Zinc acetate dihydrate | 170204   | 23637     | 40      |

- 146 529 spectra from a total of 3189 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 15 spectra from 14 *Apo-Ident* customers from 10 batches from the substance/substance group *Zinc acetate dihydrate*.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

| Supplier | Substance              | Batch    | Spectra |
|----------|------------------------|----------|---------|
| Caelo    | Zinc acetate dihydrate | 12316405 | 1       |
| Fiebig   | Zinc acetate dihydrate | 211172/2 | 1       |
| Caelo    | Zinc acetate dihydrate | 15160804 | 2       |
| Caelo    | Zinc acetate dihydrate | 15160801 | 1       |
| Caelo    | Zinc acetate dihydrate | 17020403 | 2       |
| Caelo    | Zinc acetate dihydrate | 12134801 | 2       |
| Caelo    | Zinc acetate dihydrate | 12134803 | 1       |
| Gehe     | Zinc acetate dihydrate | 12134803 | 1       |
| Caelo    | Zinc acetate dihydrate | 12316403 | 2       |
| Caelo    | Zinc acetate dihydrate | 12316404 | 1       |
| Caelo    | Zinc acetate dihydrate | 71359347 | 1       |

- 69 618 spectra from 414 *Apo-Ident* customers from a total of 23 791 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Zinc acetate dihydrate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Zinc acetate dihydrate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 156           | 44             | 146 529       |
| <b>Type C</b> | 0              | 6             | 9              | 69 618        |

The substance/substance group *Zinc acetate dihydrate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 78.0000 % (> 76.5000 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 22728     | 23030               | 2.86                         | 48.31                           |
| 23030     | 23030               | 0.00                         | 48.51                           |
| 23031     | 23031               | 0.00                         | 50.70                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **Zinc gluconate**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20379-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Zinc gluconate; Zinci gluconas; Zincum gluconicum

### Special notes

When selecting the *Zinc gluconate* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Zinc gluconate*:

| Supplier | Substance      | Batch      | Sample ID | Spectra | Certificate |
|----------|----------------|------------|-----------|---------|-------------|
| Euro OTC | Zinc gluconate | 1407033-02 | 21709     | 40      | 20140902    |
| Euro OTC | Zinc gluconate | 1508007    | 21882     | 40      | 20150827*   |
| Euro OTC | Zinc gluconate | 1603035    | 22513     | 40      | 20160427*   |
| Caelo    | Zinc gluconate | 170165     | 23034     | 40      | 20170125*   |
| Caelo    | Zinc gluconate | 170951     | 23292     | 40      | 20170518*   |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 200 spectra of 5 reference samples from the substance/substance group *Zinc gluconate*. These samples are listed above in the [calibration samples](#) section.
- 71 186 spectra from a total of 1547 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 240 spectra of 7 reference samples from the substance/substance group *Zinc gluconate*.

| Supplier | Substance      | Batch      | Sample ID          | Spectra |
|----------|----------------|------------|--------------------|---------|
| Euro OTC | Zinc gluconate | 1111002-01 | 20379              | 40      |
| Euro OTC | Zinc gluconate | 1407033-02 | 21709 <sup>†</sup> | 20      |
| Euro OTC | Zinc gluconate | 1508007    | 21882 <sup>†</sup> | 20      |
| Caelo    | Zinc gluconate | 161788     | 22619              | 40      |
| Euro OTC | Zinc gluconate | 1606018    | 22700              | 40      |
| Euro OTC | Zinc gluconate | 1701017    | 22994              | 40      |
| Euro OTC | Zinc gluconate | 1706009    | 23544              | 40      |

- 146 489 spectra from a total of 3187 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

- 5 spectra from 4 *Apo-Ident* customers from 5 batches from the substance/substance group *Zinc gluconate*.

| Supplier | Substance      | Batch            | Spectra |
|----------|----------------|------------------|---------|
| Euro OTC | Zinc gluconate | 1312010-01       | 1       |
| Euro OTC | Zinc gluconate | 1405011-01       | 1       |
| Caelo    | Zinc gluconate | 16178801         | 1       |
| Fagron   | Zinc gluconate | 14J30-B06-300520 | 1       |
| Caelo    | Zinc gluconate | 17016502         | 1       |

- 69 628 spectra from 414 *Apo-Ident* customers from a total of 23 796 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Zinc gluconate* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Zinc gluconate* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 200           | 0              | 71 186        |
| <b>Type B</b> | 0              | 240           | 0              | 146 489       |
| <b>Type C</b> | 0              | 5             | 0              | 69 628        |

The substance/substance group *Zinc gluconate* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 97.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 97.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8815 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21709     | 23292               | 3.69                         | 19.72                           |
| 21882     | 21882               | 0.00                         | 17.04                           |
| 22513     | 22513               | 0.00                         | 15.44                           |
| 23034     | 23034               | 0.00                         | 19.39                           |
| 23292     | 23292               | 0.00                         | 20.55                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group (R,S)-epinephrine hydrochloride  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20929-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

(R,S)-epinephrine hydrochloride; Adrenalinum racemici hydrochloridum

### Special notes

When selecting the (R,S)-epinephrine hydrochloride substance/substance group, the following information is displayed to the user:

- Advice for the identification of (R,S)-epinephrine hydrochloride: According to the German BfArM, ephedrine and its salts are considered as critical pharmaceuticals in compliance to German § 5 AMG. Critical pharmaceuticals must not be placed on the market or be applied to humans.

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group (R,S)-epinephrine hydrochloride:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate              |
|----------|---------------------|------------------|-----------|---------|--------------------------|
| Fagron   | (R,S)-epinephrin... | 12H08-N03        | 20929     | 40      | no certificate available |
| Fagron   | (R,S)-epinephrin... | 14A22-B05-291560 | 21567     | 40      | no certificate available |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 80 spectra of 2 reference samples from the substance/substance group (R,S)-epinephrine hydrochloride. These samples are listed above in the [calibration samples](#) section.
- 71 306 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group (R,S)-epinephrine hydrochloride.

| Supplier | Substance                       | Batch            | Sample ID          | Spectra |
|----------|---------------------------------|------------------|--------------------|---------|
| Fagron   | (R,S)-epinephrine hydrochlor... | 14A22-B05-291560 | 21567 <sup>†</sup> | 20      |
| Fagron   | (R,S)-epinephrine hydrochlor... | 16H23-B98-325052 | 22842              | 40      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 3 spectra from 3 *Apo-Ident* customers from 3 batches from the substance/substance group (R,S)-epinephrine hydrochloride.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance                       | Batch     | Spectra |
|----------|---------------------------------|-----------|---------|
| Fagron   | (R,S)-epinephrine hydrochlor... | 2021503   | 1       |
| Fagron   | (R,S)-epinephrine hydrochlor... | 14A22-B05 | 1       |
| Fagron   | (R,S)-epinephrine hydrochlor... | 10022015E | 1       |

- 69 630 spectra from 414 *Apo-Ident* customers from a total of 23 798 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

### Validation results

The validation runs checked whether the substance/substance group *(R,S)-epinephrine hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *(R,S)-epinephrine hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 80            | 0              | 71 306        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 3             | 0              | 69 630        |

The substance/substance group *(R,S)-epinephrine hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 92.5000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8817 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra ([Rule of Three](#) [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the [Mahalanobis distance](#) to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20929     | 20929               | 0.00                         | 61.11                           |
| 21567     | 21567               | 0.00                         | 62.57                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **3.4-diaminopyridine**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20317-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

3.4-diaminopyridine; 3,4-Diaminopyridinum; Amifampridinum

### Special notes

When selecting the *3.4-diaminopyridine* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *3.4-diaminopyridine*:

| Supplier | Substance           | Batch             | Sample ID | Spectra | Certificate |
|----------|---------------------|-------------------|-----------|---------|-------------|
| Fagron   | 3.4-diaminopyrid... | 13F05-N01         | 20901     | 40      | 20130606    |
| Inresa   | 3.4-diaminopyrid... | 0631350001        | 21781     | 40      | 8899        |
| Fagron   | 3.4-diaminopyrid... | 16A22-B04-317264  | 22321     | 40      | 20160204    |
| Inresa   | 3.4-diaminopyrid... | 33-15-IV-56P2749B | 22848     | 40      | 20160822    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 160 spectra of 4 reference samples from the substance/substance group *3,4-diaminopyridine*. These samples are listed above in the [calibration samples](#) section.
- 71 226 spectra from a total of 1548 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 121 spectra of 5 reference samples from the substance/substance group *3,4-diaminopyridine*.

| Supplier | Substance           | Batch            | Sample ID          | Spectra |
|----------|---------------------|------------------|--------------------|---------|
| Fagron   | 3,4-diaminopyridine | 10J14-N21        | 20317              | 40      |
| Fagron   | 3,4-diaminopyridine | 10J14-N21        | 20526              | 40      |
| Fagron   | 3,4-diaminopyridine | 13F05-N01        | 20901 <sup>†</sup> | 1       |
| Inresa   | 3,4-diaminopyridine | 631350001        | 21781 <sup>†</sup> | 20      |
| Fagron   | 3,4-diaminopyridine | 16A22-B04-317264 | 22321 <sup>†</sup> | 20      |

- 146 608 spectra from a total of 3190 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 33 spectra from 9 *Apo-Ident* customers from 19 batches from the substance/substance group *3,4-diaminopyridine*.

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

| Supplier | Substance           | Batch            | Spectra |
|----------|---------------------|------------------|---------|
| inresa   | 3.4-diaminopyridine | 58010001         | 2       |
| Inresa   | 3.4-diaminopyridine | 580710001        | 4       |
| inresa   | 3.4-diaminopyridine | 580710001        | 2       |
| inresa   | 3.4-diaminopyridine | 58710001         | 2       |
| inresa   | 3.4-diaminopyridine | 631350001        | 1       |
| Fagron   | 3.4-diaminopyridine | 15B20-B02        | 3       |
| Inresa   | 3.4-diaminopyridine | 33-15-IV-56P2749 | 2       |
| Inresa   | 3.4-diaminopyridine | 508670001        | 1       |
| Fagron   | 3.4-diaminopyridine | 11/14-N03        | 1       |
| Caelo    | 3.4-diaminopyridine | 13f05-n01        | 1       |
| Fagron   | 3.4-diaminopyridine | 11K07-N02        | 1       |
| Gehe     | 3.4-diaminopyridine | 13F07-N07        | 1       |
| Fagron   | 3.4-diaminopyridine | 13F07-N07        | 1       |
| Fagron   | 3.4-diaminopyridine | 13K14-M01        | 1       |
| Fagron   | 3.4-diaminopyridine | 13L12-M03        | 1       |
| Fagron   | 3.4-diaminopyridine | 13K14-M03        | 1       |
| Fagron   | 3.4-diaminopyridine | 13L12-M06        | 2       |
| Fagron   | 3.4-diaminopyridine | 14H11-B06        | 3       |
| Caelo    | 3.4-diaminopyridine | 14H11-B06-298447 | 2       |
| Fagron   | 3.4-diaminopyridine | 13K14-M02        | 1       |

- 69 600 spectra from 414 *Apo-Ident* customers from a total of 23 783 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *3.4-diaminopyridine* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *3.4-diaminopyridine* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 160           | 0              | 71 226        |
| <b>Type B</b> | 0              | 81            | 40             | 146 608       |
| <b>Type C</b> | 0              | 31            | 2              | 69 600        |

The substance/substance group *3.4-diaminopyridine* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate* (*specificity*) and the weighted *true positive rate* (*recognition rate*) are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9887 %) | 100.0000 % (> 96.2500 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 66.9421 % (> 64.4628 %)  |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 93.9394 % (> 84.8485 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to

exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20901     | 21781               | 7.40                         | 36.75                           |
| 21781     | 21781               | 0.00                         | 36.53                           |
| 22321     | 21781               | 4.62                         | 36.53                           |
| 22848     | 21781               | 3.69                         | 36.49                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.

# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **5-aminolevulinic acid hydrochloride**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20371-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

5-aminolevulinic acid hydrochloride; Acidi aminolevulinici hydrochloridum; Acidum aminolaevulinicum hydrochloricum

### Special notes

When selecting the *5-aminolevulinic acid hydrochloride* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *5-aminolevulinic acid hydrochloride*:

| Supplier | Substance           | Batch            | Sample ID | Spectra | Certificate |
|----------|---------------------|------------------|-----------|---------|-------------|
| Fagron   | 5-aminolevulinic... | 13K27-N02        | 21339     | 40      | 20131125    |
| Caelo    | 5-aminolevulinic... | 16357904         | 23208     | 40      | 1707616     |
| Fagron   | 5-aminolevulinic... | 17A12-B07-332960 | 23403     | 40      | 20170131    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *5-aminolevulinic acid hydrochloride*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1549 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 80 spectra of 2 reference samples from the substance/substance group *5-aminolevulinic acid hydrochloride*.

| Supplier | Substance                       | Batch            | Sample ID | Spectra |
|----------|---------------------------------|------------------|-----------|---------|
| Fagron   | 5-aminolevulinic acid hydroc... | 11I30-N01        | 20371     | 40      |
| Fagron   | 5-aminolevulinic acid hydroc... | 17A12-B07-332960 | 23404     | 40      |

- 146 649 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 33 spectra from 18 *Apo-Ident* customers from 21 batches from the substance/substance group *5-aminolevulinic acid hydrochloride*.

| Supplier | Substance                       | Batch            | Spectra |
|----------|---------------------------------|------------------|---------|
| Caelo    | 5-aminolevulinic acid hydroc... | 16E17-B08-324961 | 2       |
| Caelo    | 5-aminolevulinic acid hydroc... | 13017403         | 1       |

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| Supplier | Substance                       | Batch            | Spectra |
|----------|---------------------------------|------------------|---------|
| Fagron   | 5-aminolevulinic acid hydroc... | 13J29-N03        | 2       |
| Caelo    | 5-aminolevulinic acid hydroc... | 13K27-N02        | 1       |
| Caelo    | 5-aminolevulinic acid hydroc... | 14145003         | 2       |
| Caelo    | 5-aminolevulinic acid hydroc... | 14145007         | 1       |
| Caelo    | 5-aminolevulinic acid hydroc... | 14145011         | 1       |
| Fagron   | 5-aminolevulinic acid hydroc... | 14K04-B01-297971 | 2       |
| Caelo    | 5-aminolevulinic acid hydroc... | 15254803         | 1       |
| Fagron   | 5-aminolevulinic acid hydroc... | 7447             | 1       |
| Fagron   | 5-aminolevulinic acid hydroc... | 11I30-N01        | 1       |
| Caelo    | 5-aminolevulinic acid hydroc... | 11355616         | 1       |
| Caelo    | 5-aminolevulinic acid hydroc... | 12093205         | 2       |
| Fagron   | 5-aminolevulinic acid hydroc... | 11K09-N04        | 1       |
| Caelo    | 5-aminolevulinic acid hydroc... | 12093208         | 1       |
| Fagron   | 5-aminolevulinic acid hydroc... | 12c23-n05        | 1       |
| Fagron   | 5-aminolevulinic acid hydroc... | 12H20-N01        | 2       |
| Fagron   | 5-aminolevulinic acid hydroc... | 12K26-N05        | 2       |
| Caelo    | 5-aminolevulinic acid hydroc... | 13017402         | 1       |
| Fagron   | 5-aminolevulinic acid hydroc... | 13C19-N05        | 3       |
| Fagron   | 5-aminolevulinic acid hydroc... | 13H13-N07        | 2       |
| Fagron   | 5-aminolevulinic acid hydroc... | 13K27-N02        | 2       |

- 69 600 spectra from 414 *Apo-Ident* customers from a total of 23 780 batches from a further 696 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *5-aminolevulinic acid hydrochloride* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *5-aminolevulinic acid hydrochloride* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 80            | 0              | 146 649       |
| <b>Type C</b> | 0              | 31            | 2              | 69 600        |

The substance/substance group *5-aminolevulinic acid hydrochloride* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 92.5000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8813 %) | 93.9394 % (> 84.8485 %)  |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to

exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

### Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 21339     | 23208               | 22.16                        | 98.70                           |
| 23208     | 23208               | 0.00                         | 84.36                           |
| 23403     | 23208               | 19.36                        | 86.70                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



# VALIDATION REPORT

## IdentModul 1.3-2018-01

Validated substance/substance group **5-fluorouracil**  
Substance class APIs & excipients, solid  
Report date 19/01/2018  
Report number 20959-2018-01-19  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

5-fluorouracil; 5-Fluorouracilum

### Special notes

When selecting the *5-fluorouracil* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

978-3-7692-5416-7 *European Pharmacopoeia 8th Edition, Basic Version 2014* [3]  
Komm2.2.40 *Erfüllung von Ph. Eur. 2.2.40 durch Apo-Ident* [4]  
AA004 *Erstellung und Validierung eines IdentModul-Updates*  
Anhang F [Zusatz zu den Modellen der zweiten Stufe](#)

### Validation method

Validation is performed after every change to the chemometric model (also “database”) in three steps:

1. The chemometric model is calculated from the calibration spectra using a *PCA algorithm*. The calibration spectra originate from the calibration samples of all substances in this class.
2. In the *chemometric model* generated, the distances between all separable substances are checked for compliance with the specified safety distances.
3. All spectra are presented to the generated chemometric model for evaluation. In three runs, the reference spectra (*Type A*), spectra from independent samples (*Type B*), and spectra from the field (*Type C*) are presented successively. Here, no single *false positive* result is permitted.

Finally, a report is generated from the validation run results and is archived together with the parameters of the model generation in audit-compliant manner.

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *5-fluorouracil*:

| Supplier | Substance      | Batch              | Sample ID | Spectra | Certificate |
|----------|----------------|--------------------|-----------|---------|-------------|
| Fagron   | 5-fluorouracil | 13F19-N03          | 20959     | 40      | 1402308     |
| Fagron   | 5-fluorouracil | 13F19-N03          | 21728     | 40      | 1608169     |
| Fagron   | 5-fluorouracil | 16D01-U05/3-327376 | 23072     | 40      | 20161117    |

## Validation samples

A total of 287 748 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

**Type A** All calibration spectra.

- 120 spectra of 3 reference samples from the substance/substance group *5-fluorouracil*. These samples are listed above in the [calibration samples](#) section.
- 71 266 spectra from a total of 1550 batches from further 374 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

**Type B** Spectra from independent samples not included in the database structure. Measurement is carried out by *HiperScan GmbH*.

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the package differs. In the following table spectra recorded from the same package as the corresponding calibration samples (*Type A*) are highlighted by <sup>†</sup>.

- 60 spectra of 2 reference samples from the substance/substance group *5-fluorouracil*.

| Supplier | Substance      | Batch     | Sample ID          | Spectra |
|----------|----------------|-----------|--------------------|---------|
| Fagron   | 5-fluorouracil | 9D28-N12  | 20117              | 40      |
| Fagron   | 5-fluorouracil | 13F19-N03 | 21728 <sup>†</sup> | 20      |

- 146 669 spectra from a total of 3192 batches from further 862 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *Apo-Ident* customers carry out the measurements. *HiperScan GmbH* generally does not verify the information provided by the customer regarding manufacturer and batch number.

- 0 spectra from 0 *Apo-Ident* customers from 0 batches from the substance/substance group *5-fluorouracil*.
- 69 633 spectra from 414 *Apo-Ident* customers from a total of 23 801 batches from a further 697 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

<sup>†</sup>These spectra were recorded from material of the same package as the corresponding calibration spectra (*Type A*). Hence, these spectra are not independent and are not of *Type B*.

## Validation results

The validation runs checked whether the substance/substance group *5-fluorouracil* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *5-fluorouracil* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

|               | False positive | True positive | False negative | True negative |
|---------------|----------------|---------------|----------------|---------------|
| <b>Type A</b> | 0              | 120           | 0              | 71 266        |
| <b>Type B</b> | 0              | 60            | 0              | 146 669       |
| <b>Type C</b> | 0              | 0             | 0              | 69 633        |

The substance/substance group *5-fluorouracil* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

|               | Specificity              | Recognition rate         |
|---------------|--------------------------|--------------------------|
| <b>Type A</b> | 100.0000 % (> 99.9888 %) | 100.0000 % (> 95.0000 %) |
| <b>Type B</b> | 100.0000 % (> 99.9923 %) | 100.0000 % (> 90.0000 %) |
| <b>Type C</b> | 100.0000 % (> 99.8812 %) | n/a (n/a)                |

In order to ensure that each substance is entered with the same weight irrespective of the number of spectra available, each spectrum is weighted with the reciprocal value of its number. (If several new spectra of a substance with a very distinctive spectrum are added, the values for *specificity* and *recognition rate* are safer, but are by no means idealised.)

In order to illustrate the impact of the number of spectra, a comparison is made in parentheses as to how the *specificity* or *recognition rate* would worsen if three additional incorrect results were to exist amongst the spectra (*Rule of Three* [10, 11]). The larger the number of spectra, the lower the deterioration if the three hypothetical *incorrect results* were added.

Where the number of spectra does not exceed 20, no *recognition rate* is provided.

## Identity according to identity test using NIR spectroscopy

For each substance, a certificate of the correct identity is obtained from an independent GMP-certified test laboratory. If the identity of the sample can be provided using NIR on an independently tested reference sample, in the following table the *Mahalanobis distance* to the reference sample is specified as well as the *Mahalanobis distance* to the next non-identical substance:

| Sample ID | Reference sample ID | Distance to reference sample | Distance to next foreign sample |
|-----------|---------------------|------------------------------|---------------------------------|
| 20959     | 20959               | 0.00                         | 92.88                           |
| 21728     | 21728               | 0.00                         | 68.57                           |
| 23072     | 20959               | 12.40                        | 91.08                           |

Die Identität einer Probe wird mittels NIR bestätigt, wenn der Abstand zur nächsten Fremdprobe mindestens 50 % größer ist, als der Abstand zu einer Referenzprobe, deren Identität mittels Laborprüfung belegt wurde. Dieses Kriterium wird immer in dem chemometrischen Modell betrachtet, das alle Substanzen der Substanzklasse enthält, selbst dann wenn eine Zweite Stufe eine Untergruppe von ähnlichen Substanzen auflöst und dabei die Abstände untereinander vergrößert. Die mittels NIR bestätigten Proben untermauern die statistische Streuung der originalen Referenzsubstanz, können aber keine neuen Aspekte bzw. Ausprägungsformen der Substanz hinzufügen.



## Appendix A: Additional calibration samples (*Type A*)

Substance (spectra also enter the generation of the [chemometric model](#) which cannot be identified with this model. This serves the purpose that substances which the model is not supposed to recognise are safely rejected. The spectra of these samples are entered into the validation as *Type A*. They were recorded by *HiperScan GmbH*.

The samples originate from 150 batches. From these, 5989 spectra were recorded. The calibration spectra of substances which can be identified with the model are listed respectively in the section *calibration samples* for the individual substances and do not appear again elsewhere in this list.

| Supplier  | Substance           | Batch    | Spectra | Certificate   |
|-----------|---------------------|----------|---------|---------------|
| abcr GmbH | Dimercaptosuccin... | 1005874  | 39      | from supplier |
| abcr GmbH | Glycyrrhizic acid   | 1222024  | 40      | from supplier |
| Caelo     | Amphetamine sulf... | 13344603 | 40      | 0814J-03361   |
| Caelo     | Amphetamine sulf... | 16153902 | 40      | 2017A-03361   |
| Caelo     | Amphetamine sulf... | 13344603 | 40      | 0814J-03361   |
| Caelo     | Buprenorphine hy... | 16143001 | 40      | 2017A-07774   |
| Caelo     | Buprenorphine hy... | 12172908 | 40      | 0814I-07774   |
| Caelo     | Buprenorphine hy... | 12172908 | 40      | 0814I-07774   |
| Caelo     | Cocaine hydrochl... | 15224802 | 40      | 1316Q-01278   |
| Caelo     | Cocaine hydrochl... | 17003902 | 40      | 1917S-01278   |
| Caelo     | Cocaine hydrochl... | 13259305 | 40      | 0814J-01278   |
| Caelo     | Cocaine hydrochl... | 13259305 | 40      | 0814J-01278   |
| Caelo     | Cocaine hydrochl... | 15224802 | 40      | 1316Q-01278   |
| Caelo     | Cocaine hydrochl... | 15224802 | 40      | 1316Q-01278   |
| Caelo     | Cocaine hydrochl... | 15224802 | 40      | 1316Q-01278   |
| Caelo     | Codeine phosphat... | 13071504 | 40      | 0814J-01279   |
| Caelo     | Codeine phosphat... | 15350703 | 40      | 1316R-01279   |
| Caelo     | Codeine phosphat... | 15350703 | 30      | 1316R-01279   |
| Caelo     | Codeine phosphat... | 13071504 | 40      | 0814J-01279   |
| Caelo     | Dihydrocodeine h... | 15295901 | 40      | 1316Q-03065   |
| Caelo     | Dihydrocodeine h... | 15295901 | 40      | 1316Q-03065   |
| Caelo     | Dihydrocodeine h... | 12142506 | 40      | 0914B-03065   |
| Caelo     | Dihydrocodeine h... | 13267601 | 40      | 0914A-03065   |
| Caelo     | Dihydrocodeine h... | 13267601 | 40      | 0914A-03065   |
| Caelo     | Dihydrocodeine h... | 12142506 | 40      | 0914B-03065   |
| Caelo     | Hydromorphone hy... | 13267702 | 40      | 0914A-01334   |
| Caelo     | Hydromorphone hy... | 15393602 | 40      | 1516J-01334   |
| Caelo     | Hydromorphone hy... | 13267702 | 40      | 0914A-01334   |
| Caelo     | Hydromorphone hy... | 15393602 | 40      | 1516J-01334   |
| Caelo     | Methadone hydroc... | 15244715 | 40      | 1516A-02949   |
| Caelo     | Methadone hydroc... | 12344818 | 40      | 0914E-02949   |
| Caelo     | Methadone hydroc... | 12344818 | 40      | 0914E-02949   |
| Caelo     | Methadone hydroc... | 15244715 | 40      | 1516A-02949   |
| Caelo     | Midazolam hydroc... | 15224602 | 40      | 1516B-03538   |
| Caelo     | Midazolam hydroc... | 12215811 | 40      | 0914E-03538   |
| Caelo     | Midazolam hydroc... | 12215811 | 40      | 0914E-03538   |
| Caelo     | Midazolam hydroc... | 15224602 | 40      | 1516B-03538   |
| Caelo     | Morphine hydroch... | 15439404 | 40      | 1416R-01879   |
| Caelo     | Morphine hydroch... | 13125207 | 40      | 0914E-01879   |
| Caelo     | Morphine hydroch... | 15439404 | 40      | 1416R-01879   |
| Caelo     | Morphine hydroch... | 13349505 | 40      | 0914F-01879   |
| Caelo     | Morphine hydroch... | 16184605 | 40      | 1917S-01879   |
| Caelo     | Morphine hydroch... | 13349505 | 40      | 0914F-01879   |
| Caelo     | Morphine hydroch... | 13125207 | 40      | 0914E-01879   |
| Caelo     | Morphine sulfate    | 11333103 | 40      | 0914E-07776   |
| Caelo     | Morphine sulfate    | 15255703 | 40      | 1416Q-07776   |
| Caelo     | Morphine sulfate    | 12153212 | 40      | 0914F-07776   |
| Caelo     | Morphine sulfate    | 15255703 | 40      | 1416Q-07776   |

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| Supplier | Substance           | Batch            | Spectra | Certificate   |
|----------|---------------------|------------------|---------|---------------|
| Caelo    | Morphine sulfate    | 11333103         | 40      | 0914E-07776   |
| Caelo    | Oxycodone hydroc... | 12268914         | 40      | 1416Q-07734   |
| Caelo    | Oxycodone hydroc... | 12268913         | 40      | 1416R-07734   |
| Caelo    | Oxycodone hydroc... | 12268908         | 40      | 0914E-07734   |
| Caelo    | Oxycodone hydroc... | 12268914         | 40      | 1416Q-07734   |
| Caelo    | Oxycodone hydroc... | 12268913         | 40      | 1416R-07734   |
| Caelo    | Oxycodone hydroc... | 12034515         | 40      | 0914F-07734   |
| Caelo    | Oxycodone hydroc... | 12268908         | 40      | 0914E-07734   |
| Caelo    | Oxycodone hydroc... | 12034515         | 40      | 0914F-07734   |
| Caelo    | Phenobarbital       | 12173202         | 40      | 0914E-01040   |
| Caelo    | Phenobarbital       | 12173202         | 40      | 0914E-01040   |
| Dr. Behr | L-carnitine hydr... | WE11030091       | 40      | from supplier |
| Dr. Behr | L-carnitine tart... | WE15080050       | 40      | from supplier |
| Dr. Behr | L-carnitine tart... | WE11060069       | 40      | from supplier |
| Euro OTC | Griffonia seed e... | 1705007          | 40      | 20170601*     |
| Euro OTC | Griffonia seed e... | 1205027          | 40      | from supplier |
| Euro OTC | L-carnitine tart... | 1302017-01       | 40      | from supplier |
| Fagron   | Amphetamine sulf... | 15L01-B05-315291 | 40      | 1316Q-03361   |
| Fagron   | Amphetamine sulf... | 13G08-N11        | 40      | 0814K-03361   |
| Fagron   | Amphetamine sulf... | 13G08-N11        | 40      | 0814K-03361   |
| Fagron   | Amphetamine sulf... | 15L01-B05-315291 | 40      | 1316Q-03361   |
| Fagron   | Barbital sodium     | 14K14-B04-303353 | 40      | 1516I-07775   |
| Fagron   | Barbital sodium     | 12F27-N02        | 40      | 0814I-07775   |
| Fagron   | Barbital sodium     | 14K14-B04-303353 | 40      | 1516I-07775   |
| Fagron   | Barbital sodium     | 12F27-N02        | 40      | 0814I-07775   |
| Fagron   | Cocaine hydrochl... | 13I17-N02        | 40      | 0814I-01278   |
| Fagron   | Cocaine hydrochl... | 13I17-N02        | 40      | 0814I-01278   |
| Fagron   | Codeine monohydr... | 12C05-N05        | 40      | 0814I-01280   |
| Fagron   | Codeine monohydr... | 12C05-N05        | 40      | 0814I-01280   |
| Fagron   | Codeine phosphat... | 13C11-N10        | 40      | 0814I-01279   |
| Fagron   | Codeine phosphat... | 16E17-B05-324109 | 40      | 2017A-01279   |
| Fagron   | Codeine phosphat... | 13C11-N10        | 40      | 0814I-01279   |
| Fagron   | Codeine phosphat... | 15F09-B02-310520 | 40      | 1316Q-01279   |
| Fagron   | Codeine phosphat... | 15F09-B02-310520 | 40      | 1316Q-01279   |
| Fagron   | Dexamphetamine s... | 13I23-N01        | 40      | 0814M-03582   |
| Fagron   | Dexamphetamine s... | 13I23-N01        | 40      | 0814M-03582   |
| Fagron   | Dexamphetamine s... | 15H06-B04-313862 | 40      | 1316Q-03582   |
| Fagron   | Dexamphetamine s... | 15H06-B04-313862 | 40      | 1316Q-03582   |
| Fagron   | Dexamphetamine s... | 16D20-B01-321049 | 40      | 2017B-03582   |
| Fagron   | Dihydrocodeine h... | 13H19-N03        | 40      | 0914C-03065   |
| Fagron   | Dihydrocodeine h... | 13H19-N03        | 40      | 0914C-03065   |
| Fagron   | Dihydrocodeine h... | 15F18-B07-323388 | 40      | 2017A-03065   |
| Fagron   | Dihydrocodeine h... | 14K26-B04-306298 | 40      | 1516I-03065   |
| Fagron   | Fentanyl citrate    | 13G30-N06        | 40      | 0814M-07678   |
| Fagron   | Fentanyl citrate    | 15F18-B01-525166 | 40      | 1316Q-03686   |
| Fagron   | Fentanyl citrate    | 15F18-B01-525166 | 40      | 1316Q-03686   |
| Fagron   | Fentanyl citrate    | 15F18-B01-525098 | 40      | 1316R-03686   |
| Fagron   | Fentanyl citrate    | 13G30-N06        | 40      | 0814M-07678   |
| Fagron   | Fentanyl citrate    | 15F18-B01-525098 | 40      | 1316R-03686   |
| Fagron   | Hydromorphone hy... | 13E16-N02        | 40      | 0914B-01334   |
| Fagron   | Hydromorphone hy... | 13I25-N05        | 40      | 1516I-01334   |
| Fagron   | Hydromorphone hy... | 15L08-B08-316877 | 40      | 1917Q-01334   |
| Fagron   | Hydromorphone hy... | 13E16-N02        | 40      | 0914B-01334   |
| Fagron   | Hydromorphone hy... | 13I25-N05        | 40      | 1516I-01334   |
| Fagron   | Methadone hydroc... | 15E29-B02-313098 | 40      | 1516B-02949   |
| Fagron   | Methadone hydroc... | 16F24-B02-323183 | 40      | 1917Q-02949   |
| Fagron   | Methadone hydroc... | 13J24-B06        | 40      | 0914F-02949   |
| Fagron   | Methadone hydroc... | 13J24-B06        | 40      | 0914F-02949   |
| Fagron   | Methadone hydroc... | 15E29-B02-313098 | 40      | 1516B-02949   |
| Fagron   | Midazolam           | 14C12-B31-313222 | 40      | 1516A-07393   |

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| Supplier         | Substance           | Batch            | Spectra | Certificate   |
|------------------|---------------------|------------------|---------|---------------|
| Fagron           | Midazolam           | 13K05-N01        | 40      | 0914E-07393   |
| Fagron           | Midazolam           | 14C12-B31-313222 | 40      | 1516A-07393   |
| Fagron           | Midazolam           | 13K05-N01        | 40      | 0914E-07393   |
| Fagron           | Midazolam hydroc... | 13E22-N09        | 40      | 0914F-03538   |
| Fagron           | Midazolam hydroc... | 14L23-B04-300245 | 40      | 1516A-03538   |
| Fagron           | Midazolam hydroc... | 14L23-B04-300245 | 40      | 1516A-03538   |
| Fagron           | Midazolam hydroc... | 15H04-B03-314396 | 40      | 1917R-03538   |
| Fagron           | Midazolam hydroc... | 13E22-N09        | 40      | 0914F-03538   |
| Fagron           | Morphine hydroch... | 13G08-N04        | 40      | 0914G-01879   |
| Fagron           | Morphine hydroch... | 15I09-B08-312694 | 40      | 1416Q-01879   |
| Fagron           | Morphine hydroch... | 15I09-B08-312694 | 40      | 1416Q-01879   |
| Fagron           | Morphine hydroch... | 13G08-N04        | 40      | 0914G-01879   |
| Fagron           | Morphine sulfate    | 13J07-N04        | 40      | 0914G-07776   |
| Fagron           | Morphine sulfate    | 13J07-N04        | 40      | 0914G-07776   |
| Fagron           | Phenobarbital       | 15G07-B06-311718 | 40      | 1416Q-01040   |
| Fagron           | Phenobarbital       | 15G07-B06-311718 | 40      | 1416Q-01040   |
| Flora Apothek... | Amygdalin           | 13121802         | 40      | 1405619       |
| Flora Apothek... | Calcium colamine... | 14384            | 40      | from supplier |
| Safic-Alcan      | Amygdalin, bitte... | BAE150902        | 40      | from supplier |
| Safic-Alcan      | Amygdalin, bitte... | BAE150902        | 40      | from supplier |
| Safic-Alcan      | Dimercaptosuccin... | 20170210         | 40      | from supplier |
| Th. Geyer        | Amphetamine sulf... | 67002            | 40      | 0814I-03361   |
| Th. Geyer        | Amphetamine sulf... | 67002            | 40      | 0814I-03361   |
| Th. Geyer        | Calcium colamine... | 33299            | 40      | from supplier |
| Th. Geyer        | Cocaine hydrochl... | 60145            | 40      | 0814K-01278   |
| Th. Geyer        | Cocaine hydrochl... | 60145            | 40      | 0814K-01278   |
| Th. Geyer        | Codeine phosphat... | 67038            | 40      | 0814K-01279   |
| Th. Geyer        | Codeine phosphat... | 67038            | 40      | 0814K-01279   |
| Th. Geyer        | Dihydrocodeine h... | 67035            | 40      | 0914D-03065   |
| Th. Geyer        | Dihydrocodeine h... | 67035            | 40      | 0914D-03065   |
| Th. Geyer        | Dihydrocodeine h... | 067052           | 40      | 2017D-03065   |
| Th. Geyer        | Methadone hydroc... | 67047            | 40      | 0914H-02949   |
| Th. Geyer        | Methadone hydroc... | 67033            | 40      | 0914G-02949   |
| Th. Geyer        | Methadone hydroc... | 67047            | 40      | 0914H-02949   |
| Th. Geyer        | Methadone hydroc... | 67033            | 40      | 0914G-02949   |
| Th. Geyer        | Mg-Ca-K colamine... | 46816            | 40      | from supplier |
| Th. Geyer        | Mg-Ca-K colamine... | 36985            | 40      | from supplier |
| Th. Geyer        | Morphine hydroch... | 67036            | 40      | 0914H-01879   |
| Th. Geyer        | Morphine hydroch... | 67036            | 40      | 0914H-01879   |
| Th. Geyer        | Phenobarbital       | 67045            | 40      | 0914F-01040   |
| Th. Geyer        | Phenobarbital       | 067056           | 40      | 2017A-01040   |
| Th. Geyer        | Phenobarbital       | 67045            | 40      | 0914F-01040   |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.





## Appendix B: Additional validation samples (*Type B*)

It is necessary that spectra also enter the validation which cannot be identified with this model. In this manner, it is verified that the model also rejects unknown substances. The spectra for these samples were recorded by *HiperScan GmbH*. They are allocated to the *Type B*. They also include the calibration spectra for other models.

The samples originate from 1563 batches. From these 67 404 spectra were recorded. The spectra recorded on independent samples of substances which can be identified with the model are listed respectively in the section *Type B* for the individual substances and do not appear again elsewhere in this list.

| Supplier         | Substance           | Batch          | Spectra | Certificate        |
|------------------|---------------------|----------------|---------|--------------------|
| abcr GmbH        | Amygdalin           | 1310579        | 40      | not necessary      |
| abcr GmbH        | Amygdalin           | 1310927        | 40      | not necessary      |
| Alfa Aesar       | Theobromine, 99%    | A11861         | 44      | not available      |
| AppliChem        | Papain              | 1G000215       | 40      | 1407433            |
| Audor            | Dithranole          | pending        | 49      | AR-12-FG-003000-01 |
| Aurica           | Rosemary leaf, cut  | 521306257      | 60      | not necessary      |
| Auropure Life... | Amygdalin, bitte... | PA02099-160822 | 30      | from supplier      |
| Berco            | Maltodextrin        | 445-11         | 40      | not available      |
| Biogenerics      | Dimercaptosuccin... | 100805         | 40      | from supplier      |
| Bombastus        | Acorus root, nat... | 272703         | 40      | not necessary      |
| Bombastus        | Bean shells, cut    | 00263386       | 40      | from supplier      |
| Bombastus        | Bitter fennel       | 289870         | 60      | AR-15-FG-008161-01 |
| Bombastus        | Blessed thistle,... | 00244795       | 40      | AR-12-FG-007244-01 |
| Bombastus        | Coltsfoot leaf, ... | 00232644       | 40      | from supplier      |
| Bombastus        | Coltsfoot leaf, ... | 00263091       | 40      | not necessary      |
| Bombastus        | Coltsfoot leaf, ... | 00263091       | 40      | not necessary      |
| Bombastus        | Kelp, cut           | 272383         | 40      | 1406341            |
| Bombastus        | Liquorice root, ... | 270853         | 40      | not necessary      |
| Bombastus        | Maize style, cut    | 274920         | 40      | not necessary      |
| Bombastus        | Marshmallow root... | 00267759       | 40      | not necessary      |
| Bombastus        | Matricaria flower   | 268712         | 40      | not necessary      |
| Bombastus        | Matricaria flower   | 270808         | 40      | from supplier      |
| Bombastus        | Oak bark, cut       | 00254077       | 40      | not necessary      |
| Bombastus        | Peppermint leaf,... | 275295         | 40      | not necessary      |
| Bombastus        | Sage leaf, cut      | pending        | 40      | not necessary      |
| Bombastus        | Tall golden rod,... | 270047         | 40      | not necessary      |
| Bombastus        | Thyme, rubbed       | pending        | 20      | not necessary      |
| Bombastus        | Valerian root, cut  | pending        | 20      | not necessary      |
| Bombastus        | Wild pansy, cut     | 00262174       | 50      | not necessary      |
| Bombastus        | Willow bark, cut    | 00263841       | 40      | AR-12-FG-008662-01 |
| Bombastus        | Yarrow herb, cut    | 00266775       | 40      | not necessary      |
| Bombastus        | Yarrow herb, cut    | 00263526       | 40      | not necessary      |
| Caelo            | Acorus root, nat... | 12076404       | 40      | not necessary      |
| Caelo            | Acorus root, pee... | 12295902       | 40      | not necessary      |
| Caelo            | Acorus root, pee... | 11054204       | 80      | not necessary      |
| Caelo            | Acorus root, pee... | 83244289       | 80      | F 2009 001 075     |
| Caelo            | Acorus root, pee... | 10180804       | 50      | from supplier      |
| Caelo            | Acorus root, pee... | 12239001       | 40      | not necessary      |
| Caelo            | Agarikon            | 14190706       | 60      | not necessary      |
| Caelo            | Agarikon            | 13130602       | 48      | 1405003            |
| Caelo            | Agarikon            | 14190702       | 60      | not necessary      |
| Caelo            | Agarikon            | 11024502       | 30      | not necessary      |
| Caelo            | Agnus castus fruit  | 13193401       | 40      | AR-15-FG-006453-01 |
| Caelo            | Agnus castus fruit  | 15318705       | 60      | pending            |
| Caelo            | Agnus castus fruit  | 12274003       | 40      | 1501649            |
| Caelo            | Agrimony, cut       | 11374004       | 40      | not necessary      |
| Caelo            | Agrimony, cut       | 10325505       | 45      | not necessary      |
| Caelo            | Agrimony, cut       | 09300101       | 40      | not necessary      |

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| Supplier | Substance           | Batch    | Spectra | Certificate        |
|----------|---------------------|----------|---------|--------------------|
| Caelo    | Alchemilla alpin... | 12147201 | 40      | not necessary      |
| Caelo    | Alchemilla, cut     | 81938349 | 70      | F 2009 001 043     |
| Caelo    | Alchemilla, cut     | 12153306 | 40      | not necessary      |
| Caelo    | Allspice, powder... | 12042703 | 40      | not necessary      |
| Caelo    | Almonds, bitter,... | 13220401 | 40      | 1406296            |
| Caelo    | Aloes, cape, cut    | 11048808 | 40      | 1404398            |
| Caelo    | Aloes, cape, cut    | 11048808 | 40      | pending            |
| Caelo    | Aloes, cape, cut    | 14087106 | 60      | pending            |
| Caelo    | Aloes, cape, pow... | 12183008 | 40      | not necessary      |
| Caelo    | Aloes, cape, pow... | 11132115 | 39      | not necessary      |
| Caelo    | Aloes, cape, pow... | 10237705 | 50      | not necessary      |
| Caelo    | Aloes, cape, pow... | 11132107 | 40      | not necessary      |
| Caelo    | Aloes, cape, pow... | 11132115 | 30      | 1404400            |
| Caelo    | Aloes, cape, pow... | 09286307 | 40      | not necessary      |
| Caelo    | Aluminium chlori... | 10026113 | 40      | not necessary      |
| Caelo    | Aluminium oxide,... | 12163019 | 40      | not necessary      |
| Caelo    | Aluminium oxide,... | 13119121 | 40      | not necessary      |
| Caelo    | Aluminium potass... | 12144605 | 40      | from supplier      |
| Caelo    | Aluminium potass... | 10079208 | 40      | from supplier      |
| Caelo    | American liverwo... | 11254605 | 40      | not necessary      |
| Caelo    | Ammonium chloride   | 12356101 | 40      | not necessary      |
| Caelo    | Ammonium chloride   | 10176319 | 40      | AR-13-FG-001330-01 |
| Caelo    | Ammonium hydroge... | 81675468 | 40      | not necessary      |
| Caelo    | Amphetamine sulf... | 13344603 | 20      | 0814J-03361        |
| Caelo    | Amphetamine sulf... | 16153902 | 40      | 2017A-03361        |
| Caelo    | Angelica root       | 12080409 | 40      | not necessary      |
| Caelo    | Angelica root       | 10200705 | 50      | not necessary      |
| Caelo    | Angelica root       | 12168701 | 40      | pending            |
| Caelo    | Angelica root       | 09030301 | 70      | F 2009 001 059     |
| Caelo    | Angelica root       | 12080404 | 40      | 1403053            |
| Caelo    | Aniseed             | 11370301 | 40      | not necessary      |
| Caelo    | Aniseed             | 09325104 | 80      | F 2010 000 053     |
| Caelo    | Aniseed             | 13333903 | 40      | not necessary      |
| Caelo    | Aniseed             | 11370301 | 40      | pending            |
| Caelo    | Aniseed, pounded    | 11242001 | 40      | not necessary      |
| Caelo    | Aniseed, pounded    | 13357101 | 40      | not necessary      |
| Caelo    | Aniseed, pounded    | 12111301 | 40      | not necessary      |
| Caelo    | Aniseed, powdered   | 11306208 | 40      | not necessary      |
| Caelo    | Aniseed, powdered   | 11306203 | 40      | not necessary      |
| Caelo    | Aniseed, powdered   | 11306204 | 40      | AR-12-FG-007324-02 |
| Caelo    | Apple, cut          | 11229807 | 60      | from supplier      |
| Caelo    | Arnica flower       | 11259801 | 40      | not necessary      |
| Caelo    | Arnica flower       | 11285702 | 40      | not necessary      |
| Caelo    | Arnica flower       | 10187404 | 40      | not necessary      |
| Caelo    | Artichoke leaf, ... | 11020602 | 30      | not necessary      |
| Caelo    | Artichoke leaf, ... | 12173302 | 40      | not necessary      |
| Caelo    | Artichoke leaf, ... | 11020601 | 40      | not necessary      |
| Caelo    | Artichoke leaf, ... | 11020602 | 40      | AR-12-FG-007243-01 |
| Caelo    | Artichoke leaf, ... | 13310707 | 40      | not necessary      |
| Caelo    | Ash leaf, cut       | 09344910 | 40      | AR-12-FG-008592-01 |
| Caelo    | Ash leaf, cut       | 11031303 | 40      | not necessary      |
| Caelo    | Asparagus root, ... | 10299012 | 30      | pending            |
| Caelo    | Asparagus root, ... | 10299010 | 40      | pending            |
| Caelo    | Barberries          | 12217109 | 60      | pending            |
| Caelo    | Barberries          | 14057312 | 60      | 1508391            |
| Caelo    | Barberries          | 11058309 | 40      | pending            |
| Caelo    | Barberry root ba... | 12112601 | 40      | not necessary      |
| Caelo    | Barium sulfate      | 171113   | 20      | 20170509*          |
| Caelo    | Basil, rubbed       | 12066404 | 60      | not necessary      |
| Caelo    | Basil, rubbed       | 12007004 | 40      | not necessary      |

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| Supplier | Substance             | Batch    | Spectra | Certificate        |
|----------|-----------------------|----------|---------|--------------------|
| Caelo    | Bean shells, cut      | 11030601 | 60      | not necessary      |
| Caelo    | Bean shells, cut      | 08301006 | 40      | not necessary      |
| Caelo    | Bearberry leaf, ...   | 12186502 | 40      | not necessary      |
| Caelo    | Bearberry leaf, ...   | 91701269 | 80      | F 2009 001 028     |
| Caelo    | Bentonite             | 12237603 | 40      | not necessary      |
| Caelo    | Bentonite             | 11304413 | 30      | not necessary      |
| Caelo    | Bentonite             | pending  | 40      | AR-14-FG-000423-01 |
| Caelo    | Bentonite             | 11304413 | 40      | not necessary      |
| Caelo    | Benzalkonium chl. ... | 16171603 | 30      | not necessary      |
| Caelo    | Betony herb, cut      | 12007205 | 40      | not necessary      |
| Caelo    | Betony herb, cut      | 09286401 | 70      | F 2010 000 059     |
| Caelo    | Betony herb, cut      | 12007201 | 40      | not necessary      |
| Caelo    | Betony herb, cut      | 12007205 | 60      | not necessary      |
| Caelo    | Bilberry fruit, ...   | 92996429 | 70      | F 2009 001 041     |
| Caelo    | Bilberry fruit, ...   | 10265602 | 40      | not necessary      |
| Caelo    | Bilberry leaf, cut    | 12140206 | 40      | not necessary      |
| Caelo    | Bilberry leaf, cut    | 90715249 | 70      | F 2010 000 050     |
| Caelo    | Birch leaf, cut       | 83445179 | 70      | F 2009 001 022     |
| Caelo    | Birch leaf, cut       | 12193105 | 40      | not necessary      |
| Caelo    | Bitter fennel         | 17020610 | 40      | 1708048            |
| Caelo    | Bitter fennel         | 161603   | 60      | 20160718*          |
| Caelo    | Bitter fennel         | 91036399 | 61      | F 2009 001 040     |
| Caelo    | Bitter fennel         | 14376403 | 60      | not necessary      |
| Caelo    | Bitter fennel         | 13413702 | 40      | 1412549            |
| Caelo    | Bitter fennel         | 12167102 | 40      | not necessary      |
| Caelo    | Bitter fennel         | 12094708 | 30      | pending            |
| Caelo    | Bitter fennel         | 11016310 | 30      | not necessary      |
| Caelo    | Bitter fennel         | 11185504 | 80      | not necessary      |
| Caelo    | Bitter fennel         | 10109004 | 40      | not necessary      |
| Caelo    | Bitter fennel         | 12094703 | 30      | not necessary      |
| Caelo    | Bitter fennel         | 11016318 | 40      | not necessary      |
| Caelo    | Bitter fennel         | 1019009  | 40      | not necessary      |
| Caelo    | Bitter orange fl. ... | 12266605 | 40      | not necessary      |
| Caelo    | Bitter orange fl. ... | pending  | 40      | not necessary      |
| Caelo    | Bitter orange fl. ... | 11049306 | 75      | not necessary      |
| Caelo    | Bitter orange fl. ... | 12266703 | 40      | not necessary      |
| Caelo    | Bitter orange fl. ... | 11049212 | 40      | not necessary      |
| Caelo    | Bitter orange fl. ... | 11049201 | 40      | not necessary      |
| Caelo    | Bitter orange fl. ... | 11049211 | 40      | not necessary      |
| Caelo    | Bitter orange pe. ... | 12067402 | 40      | not necessary      |
| Caelo    | Bitter orange pe. ... | 12067402 | 40      | not necessary      |
| Caelo    | Bitter orange pe. ... | 12067405 | 40      | not necessary      |
| Caelo    | Black cohosh, cut     | 10281114 | 40      | not necessary      |
| Caelo    | Black cohosh, cut     | 13237903 | 40      | not necessary      |
| Caelo    | Black cohosh, cut     | 10281112 | 40      | not necessary      |
| Caelo    | Black cohosh, cut     | 13237901 | 40      | pending            |
| Caelo    | Black cumin seed      | 10121916 | 40      | not necessary      |
| Caelo    | Black cumin seed      | 11233503 | 40      | 1403495            |
| Caelo    | Black cumin seed      | 10121913 | 40      | not necessary      |
| Caelo    | Black cumin seed      | 161157   | 60      | not necessary      |
| Caelo    | Black mustard seed    | 12189303 | 40      | 1403472            |
| Caelo    | Black mustard seed    | 15120405 | 60      | AR-17-FG-007964-01 |
| Caelo    | Black mustard seed    | 11124307 | 40      | not necessary      |
| Caelo    | Black mustard se. ... | 16051807 | 60      | 9887               |
| Caelo    | Black mustard se. ... | 13358304 | 40      | pending            |
| Caelo    | Black mustard se. ... | 12350204 | 80      | 1403711            |
| Caelo    | Black mustard se. ... | 10064103 | 40      | not necessary      |
| Caelo    | Black mustard se. ... | 12009703 | 40      | not necessary      |
| Caelo    | Black mustard se. ... | 12009703 | 40      | not necessary      |
| Caelo    | Black pepper          | 12192311 | 40      | 1403490            |

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| Supplier | Substance           | Batch    | Spectra | Certificate        |
|----------|---------------------|----------|---------|--------------------|
| Caelo    | Black pepper        | 13221114 | 40      | not necessary      |
| Caelo    | Black pepper        | 11193905 | 40      | not necessary      |
| Caelo    | Black pepper        | 11193906 | 40      | not necessary      |
| Caelo    | Blackberry leaf,... | 10136403 | 40      | not necessary      |
| Caelo    | Blackberry leaf,... | 08327407 | 60      | not necessary      |
| Caelo    | Blackberry leaf,... | 10136407 | 40      | AR-12-FG-008205-01 |
| Caelo    | Blackberry leaf,... | 11030707 | 40      | not necessary      |
| Caelo    | Blackcurrant lea... | 12168804 | 40      | not necessary      |
| Caelo    | Blackcurrant lea... | 09373908 | 40      | not necessary      |
| Caelo    | Blackcurrants       | 12272801 | 40      | 1403468            |
| Caelo    | Blackcurrants       | 14212502 | 60      | not necessary      |
| Caelo    | Blackcurrants       | 14212509 | 60      | 20140829           |
| Caelo    | Blackthorn flower   | 12178101 | 40      | not necessary      |
| Caelo    | Blessed thistle,... | 12038203 | 40      | not necessary      |
| Caelo    | Blessed thistle,... | 09355201 | 40      | not necessary      |
| Caelo    | Blessed thistle,... | 12038203 | 40      | not necessary      |
| Caelo    | Blue bottle flow... | 13241902 | 60      | AR-15-FG-005838-01 |
| Caelo    | Blue bottle flow... | 10291105 | 40      | pending            |
| Caelo    | Blue bottle flow... | 10291110 | 40      | pending            |
| Caelo    | Bogbean leaf, cut   | 12226101 | 40      | not necessary      |
| Caelo    | Boldo leaf, cut     | 13367904 | 40      | not necessary      |
| Caelo    | Boldo leaf, cut     | 10027509 | 40      | not necessary      |
| Caelo    | Borage herb, cut    | 11206712 | 40      | not necessary      |
| Caelo    | Bucho leaf          | 12034903 | 40      | not necessary      |
| Caelo    | Buckwheat herb, ... | 11212806 | 40      | not necessary      |
| Caelo    | Buprenorphine hy... | 10242705 | 40      | not necessary      |
| Caelo    | Buprenorphine hy... | 16143001 | 40      | 2017A-07774        |
| Caelo    | Buprenorphine hy... | 12172908 | 20      | 0814I-07774        |
| Caelo    | Burdock root, cut   | 11100801 | 40      | not necessary      |
| Caelo    | Burdock root, cut   | 82227239 | 80      | F 2009 001 060     |
| Caelo    | Burnet root         | 09331503 | 40      | not necessary      |
| Caelo    | Burnet root         | 12024406 | 40      | not necessary      |
| Caelo    | Burnet root         | 12027407 | 40      | not necessary      |
| Caelo    | Burnet root         | 12027410 | 40      | not necessary      |
| Caelo    | Calcium chloride... | 10103114 | 40      | not necessary      |
| Caelo    | Calcium hydrogen... | 10135201 | 40      | not necessary      |
| Caelo    | Calcium sulfate ... | 10132401 | 40      | not necessary      |
| Caelo    | Calcium sulfate ... | 09246306 | 40      | not necessary      |
| Caelo    | Calendula flower    | 11221404 | 40      | not necessary      |
| Caelo    | Calendula flower... | 11187605 | 40      | not necessary      |
| Caelo    | Calendula flower... | 09157609 | 40      | not necessary      |
| Caelo    | Calendula flower... | 11187605 | 40      | not necessary      |
| Caelo    | Calendula flower... | 10118307 | 50      | not necessary      |
| Caelo    | Campeche wood       | 11074108 | 40      | from supplier      |
| Caelo    | Campeche wood       | 11074105 | 40      | from supplier      |
| Caelo    | Caraway fruit       | 13397104 | 40      | AR-15-FG-001526-01 |
| Caelo    | Caraway fruit       | 11003217 | 40      | not necessary      |
| Caelo    | Caraway fruit       | 13397104 | 60      | AR-15-FG-001527-01 |
| Caelo    | Caraway fruit       | 09334905 | 80      | AR-12-FG-002707-01 |
| Caelo    | Caraway fruit       | 09267814 | 40      | not necessary      |
| Caelo    | Caraway fruit       | 13306006 | 60      | AR-16-FG-000540-03 |
| Caelo    | Caraway fruit       | 09267825 | 40      | not necessary      |
| Caelo    | Caraway fruit       | 11003201 | 40      | not necessary      |
| Caelo    | Caraway fruit       | 09267816 | 50      | not necessary      |
| Caelo    | Caraway fruit       | 09267815 | 40      | AR-12-FG-007975-01 |
| Caelo    | Caraway fruit       | 15097115 | 60      | AR-17-FG-006649-01 |
| Caelo    | Caraway fruit, p... | 12116901 | 40      | 1403469            |
| Caelo    | Caraway fruit, p... | 12116904 | 40      | not necessary      |
| Caelo    | Caraway fruit, p... | 16073201 | 60      | AR-17-FG-006648-01 |
| Caelo    | Caraway fruit, p... | 13367101 | 40      | not necessary      |

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| Supplier | Substance           | Batch    | Spectra | Certificate        |
|----------|---------------------|----------|---------|--------------------|
| Caelo    | Caraway fruit, p... | 14358801 | 60      | AR-15-FG-014914-01 |
| Caelo    | Carbachol           | 11150302 | 40      | 1401147            |
| Caelo    | Cardamom fruit      | 13260504 | 40      | not necessary      |
| Caelo    | Cardamom fruit      | pending  | 40      | not necessary      |
| Caelo    | Cardamom fruit      | 10285713 | 40      | not necessary      |
| Caelo    | Cardamom fruit      | 11309107 | 40      | not necessary      |
| Caelo    | Cardamom, excort... | 13026104 | 40      | 1405002            |
| Caelo    | Cardamom, excort... | 11247103 | 40      | not necessary      |
| Caelo    | Carnauba wax        | 170903   | 40      | 20170512*          |
| Caelo    | Carrageenan, cut    | 11053905 | 40      | not necessary      |
| Caelo    | Castoreum, powde... | pending  | 40      | pending            |
| Caelo    | Castoreum, powde... | 13410403 | 40      | not necessary      |
| Caelo    | Castoreum, powde... | 12137409 | 40      | 1402590            |
| Caelo    | Castoreum, powde... | 09117503 | 50      | pending            |
| Caelo    | Castoreum, powde... | 13410403 | 40      | not necessary      |
| Caelo    | Cayenne pepper, ... | 10197606 | 40      | AR-12-FG-008515-01 |
| Caelo    | Cayenne pepper, ... | 12014405 | 40      | pending            |
| Caelo    | Cayenne pepper, ... | 14103104 | 60      | not necessary      |
| Caelo    | Celery root, cut    | 10270002 | 40      | not necessary      |
| Caelo    | Centaury, cut       | 91233419 | 80      | F 2009 001 045     |
| Caelo    | Centaury, cut       | 11097602 | 40      | not necessary      |
| Caelo    | Ceylonese Cinnam... | 12242810 | 40      | not necessary      |
| Caelo    | Ceylonese Cinnam... | 12242806 | 40      | 1403083            |
| Caelo    | Chelidonium maju... | 13774    | 80      | from supplier      |
| Caelo    | Chickweed, cut      | 10359112 | 40      | not necessary      |
| Caelo    | Chickweed, cut      | 13254411 | 40      | 1412550            |
| Caelo    | Chickweed, cut      | 13040502 | 40      | 1403482            |
| Caelo    | Chicory herb, cut   | 12034303 | 100     | not necessary      |
| Caelo    | Chicory herb, cut   | 09355304 | 40      | not necessary      |
| Caelo    | Chicory herb, cut   | 12354302 | 100     | not necessary      |
| Caelo    | Chicory herb, cut   | 12034303 | 40      | not necessary      |
| Caelo    | Chicory root, cut   | 11081805 | 40      | not necessary      |
| Caelo    | Chicory root, cut   | 11374504 | 40      | not necessary      |
| Caelo    | Cinchona bark, cut  | 11238512 | 40      | 1403463            |
| Caelo    | Cinchona bark, cut  | 14009304 | 40      | AR-15-FG-007677-01 |
| Caelo    | Cinchona bark, cut  | 15301903 | 60      | AR-17-FG-007831-01 |
| Caelo    | Cinchona bark, cut  | pending  | 40      | not necessary      |
| Caelo    | Cinchona bark, cut  | 13031007 | 40      | not necessary      |
| Caelo    | Cinnamon rods (C... | 11247009 | 40      | AR-12-FG-008665-01 |
| Caelo    | Cinnamon rods (C... | 13241807 | 40      | not necessary      |
| Caelo    | Cinnamon, cut       | 13304414 | 40      | not necessary      |
| Caelo    | Cinnamon, cut       | 11221004 | 40      | AR-12-FG-008664-01 |
| Caelo    | Cinnamon, cut       | 12309902 | 40      | pending            |
| Caelo    | Cinnamon, cut       | 16114401 | 60      | 1704441            |
| Caelo    | Cinnamon, cut       | pending  | 40      | not necessary      |
| Caelo    | Cinnamon, cut       | 14175010 | 60      | 1505349            |
| Caelo    | Clove               | 10242010 | 40      | AR-12-FG-008490-01 |
| Caelo    | Clove               | 12095805 | 40      | pending            |
| Caelo    | Clove               | 16207804 | 60      | 1708676            |
| Caelo    | Clove, powdered ... | 12355301 | 40      | 1403054            |
| Caelo    | Clove, powdered ... | 12355304 | 40      | not necessary      |
| Caelo    | Cocaine hydrochl... | 15224802 | 20      | 1316Q-01278        |
| Caelo    | Cocaine hydrochl... | 13259305 | 20      | 0814J-01278        |
| Caelo    | Cocaine hydrochl... | 16142710 | 40      | 1917T-01278        |
| Caelo    | Cocaine hydrochl... | 15224802 | 20      | 1316Q-01278        |
| Caelo    | Cocaine hydrochl... | 15224802 | 20      | 1316Q-01278        |
| Caelo    | Cocaine hydrochl... | 16142710 | 40      | 1917T-01278        |
| Caelo    | Cocaine hydrochl... | 17003902 | 40      | 1917S-01278        |
| Caelo    | Cocaine hydrochl... | 15224802 | 20      | 1316Q-01278        |
| Caelo    | Cocoa bark, cut     | 11291008 | 40      | not necessary      |

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| Supplier | Substance           | Batch    | Spectra | Certificate        |
|----------|---------------------|----------|---------|--------------------|
| Caelo    | Codeine phosphat... | 16349702 | 40      | 2017C-01279        |
| Caelo    | Codeine phosphat... | 16169807 | 40      | 2017B-01279        |
| Caelo    | Codeine phosphat... | 15350703 | 20      | 1316R-01279        |
| Caelo    | Codeine phosphat... | 13071504 | 20      | 0814J-01279        |
| Caelo    | Codeine phosphat... | 11234808 | 40      | not necessary      |
| Caelo    | Codeine phosphat... | 15350703 | 30      | 1316R-01279        |
| Caelo    | Codeine phosphat... | 16349702 | 40      | 2017C-01279        |
| Caelo    | Codeine phosphat... | 16169807 | 40      | 2017B-01279        |
| Caelo    | Common broom her... | pending  | 40      | not necessary      |
| Caelo    | Common madder ro... | 11070908 | 40      | not necessary      |
| Caelo    | Common wormwood ... | 12016705 | 40      | not necessary      |
| Caelo    | Common wormwood ... | 83410339 | 70      | F 2010 000 057     |
| Caelo    | Copper (II) sulf... | 08258803 | 40      | not necessary      |
| Caelo    | Coriander           | 13299403 | 40      | 1412548            |
| Caelo    | Coriander           | 12080904 | 40      | pending            |
| Caelo    | Coriander           | 16010212 | 60      | AR-17-FG-015965-01 |
| Caelo    | Coriander           | 11088402 | 40      | not necessary      |
| Caelo    | Coriander           | 11088402 | 40      | AR-12-FG-008489-01 |
| Caelo    | Cottonwood bud      | 12027502 | 40      | not necessary      |
| Caelo    | Cottonwood bud      | 12027505 | 40      | not necessary      |
| Caelo    | Couch grass rhiz... | 10049607 | 50      | not necessary      |
| Caelo    | Couch grass rhiz... | 12186702 | 40      | not necessary      |
| Caelo    | Couch grass rhiz... | 10049612 | 50      | not necessary      |
| Caelo    | Couch grass rhiz... | 10049612 | 40      | not necessary      |
| Caelo    | Cowberry leaf, cut  | 11334302 | 40      | not necessary      |
| Caelo    | Cowberry leaf, cut  | 11334302 | 40      | not necessary      |
| Caelo    | Cumin               | 11378308 | 40      | not necessary      |
| Caelo    | Daisy flower        | 11068306 | 40      | not necessary      |
| Caelo    | Daisy flower        | 11068301 | 40      | not necessary      |
| Caelo    | Damiana leaf, cut   | 11026606 | 40      | not necessary      |
| Caelo    | Damiana leaf, cut   | 11026608 | 40      | not necessary      |
| Caelo    | Damiana leaf, cut   | 11026609 | 40      | not necessary      |
| Caelo    | Dandelion herb w... | 10121614 | 40      | not necessary      |
| Caelo    | Dandelion herb w... | 11030305 | 40      | AR-12-FG-008590-01 |
| Caelo    | Dandelion herb w... | 07341702 | 120     | F 2009 001 050     |
| Caelo    | Dandelion herb w... | 11217109 | 40      | not necessary      |
| Caelo    | Dandelion herb w... | 11217109 | 40      | not necessary      |
| Caelo    | Dandelion root, ... | 12363102 | 40      | 1403708            |
| Caelo    | Dandelion root, ... | 13329708 | 40      | 1411089            |
| Caelo    | Dandelion root, ... | 10024710 | 40      | not necessary      |
| Caelo    | Dandelion root, ... | 10024714 | 50      | not necessary      |
| Caelo    | Dandelion root, ... | 13329701 | 40      | not necessary      |
| Caelo    | Devil's claw root   | 80278288 | 70      | F 2010 000 065     |
| Caelo    | Devil's claw root   | 13298202 | 40      | not necessary      |
| Caelo    | Devil's claw root   | 12031806 | 40      | not necessary      |
| Caelo    | Dihydrocodeine h... | 10223612 | 40      | not necessary      |
| Caelo    | Dihydrocodeine h... | 15295901 | 20      | 1316Q-03065        |
| Caelo    | Dihydrocodeine h... | 15295901 | 20      | 1316Q-03065        |
| Caelo    | Dihydrocodeine h... | 15295910 | 40      | 2017B-03065        |
| Caelo    | Dihydrocodeine h... | 16106209 | 40      | 2017C-03065        |
| Caelo    | Dihydrocodeine h... | 15295910 | 40      | 2017B-03065        |
| Caelo    | Dihydrocodeine h... | 16106209 | 40      | 2017C-03065        |
| Caelo    | Dihydrocodeine h... | 13267601 | 20      | 0914A-03065        |
| Caelo    | Dihydrocodeine h... | 12142506 | 20      | 0914B-03065        |
| Caelo    | Dill fruit          | 12342906 | 40      | not necessary      |
| Caelo    | Dill fruit          | 14018705 | 60      | pending            |
| Caelo    | Dill fruit          | 12038301 | 40      | not necessary      |
| Caelo    | Dill fruit          | 12038301 | 40      | pending            |
| Caelo    | Dill fruit          | 12289901 | 40      | 1403464            |
| Caelo    | Dill herb, cut      | 13007602 | 40      | 1402204            |

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| Supplier | Substance            | Batch    | Spectra | Certificate        |
|----------|----------------------|----------|---------|--------------------|
| Caelo    | Dill herb, cut       | 11295107 | 40      | pending            |
| Caelo    | Dill herb, cut       | 11295103 | 40      | not necessary      |
| Caelo    | Dill herb, cut       | 13007610 | 40      | not necessary      |
| Caelo    | Dithranole           | 90987209 | 32      | I 2009 000 268     |
| Caelo    | Dry beads Caelo...   | 12382203 | 40      | from supplier      |
| Caelo    | Dry beads Caelo...   | 11005804 | 40      | from supplier      |
| Caelo    | Echinacea pallid...  | 12244501 | 40      | not necessary      |
| Caelo    | Echinacea pallid...  | 14120602 | 40      | not necessary      |
| Caelo    | Elder berries        | 13367704 | 40      | 1410179            |
| Caelo    | Elder berries        | 12267807 | 40      | 1403466            |
| Caelo    | Elder flower, ru...  | 83446199 | 70      | F 2009 001 019     |
| Caelo    | Elder flower, ru...  | 12221902 | 40      | not necessary      |
| Caelo    | Elecampane rhizo...  | 12113303 | 40      | not necessary      |
| Caelo    | Elecampane rhizo...  | 11196905 | 40      | not necessary      |
| Caelo    | Eleutherococcus...   | 10381814 | 40      | not necessary      |
| Caelo    | Eleutherococcus...   | 09035506 | 50      | not necessary      |
| Caelo    | Eleutherococcus...   | 10381814 | 30      | not necessary      |
| Caelo    | Elm bark, cut        | 10347205 | 40      | not necessary      |
| Caelo    | Elm bark, cut        | 10347205 | 60      | not necessary      |
| Caelo    | Equisetum stem, ...  | 11076307 | 40      | not necessary      |
| Caelo    | Equisetum stem, ...  | 10375515 | 40      | not necessary      |
| Caelo    | Equisetum stem, ...  | 91234289 | 70      | F 2009 001 048     |
| Caelo    | Eucalyptus leaf, ... | 11307706 | 40      | not necessary      |
| Caelo    | Eucalyptus leaf, ... | 09346804 | 40      | not necessary      |
| Caelo    | Euphrasy herb, cut   | 09311412 | 50      | not necessary      |
| Caelo    | Fenugreek            | 11313204 | 40      | not necessary      |
| Caelo    | Fenugreek            | 08329901 | 70      | F 2010 000 068     |
| Caelo    | Fenugreek, powde...  | 11042306 | 40      | pending            |
| Caelo    | Fenugreek, powde...  | 12149605 | 40      | not necessary      |
| Caelo    | Fenugreek, powde...  | 11042302 | 40      | not necessary      |
| Caelo    | Fenugreek, powde...  | 15308704 | 60      | AR-17-FG-006625-01 |
| Caelo    | Fenugreek, powde...  | 11042303 | 40      | AR-12-FG-007209-01 |
| Caelo    | Ferric (III) sul...  | 10354412 | 40      | AR-13-FG-002914-01 |
| Caelo    | Flax weed herb, ...  | 09346401 | 30      | pending            |
| Caelo    | Flax weed herb, ...  | 13007505 | 40      | 1403462            |
| Caelo    | Flax weed herb, ...  | 14005309 | 60      | not necessary      |
| Caelo    | Frangula bark, cut   | 12185901 | 40      | not necessary      |
| Caelo    | Frangula bark, cut   | 10069607 | 100     | AR-12-FG-002850-01 |
| Caelo    | Frangula bark, cut   | 11254001 | 40      | not necessary      |
| Caelo    | Frankincense         | 10054608 | 40      | not necessary      |
| Caelo    | Frankincense         | 100546   | 40      | not necessary      |
| Caelo    | Frankincense         | 12120005 | 40      | 1402495            |
| Caelo    | Frankincense         | pending  | 40      | not necessary      |
| Caelo    | Frankincense         | 10349210 | 40      | not necessary      |
| Caelo    | Frankincense         | 13112801 | 40      | not necessary      |
| Caelo    | Fraxinella root, ... | 10189103 | 40      | not necessary      |
| Caelo    | Fraxinella root, ... | 14110802 | 60      | not necessary      |
| Caelo    | Fraxinella root, ... | 11314705 | 80      | not necessary      |
| Caelo    | Fraxinella root, ... | 11314705 | 40      | pending            |
| Caelo    | Fumitory, cut        | 83129399 | 69      | F 2009 001 049     |
| Caelo    | Fumitory, cut        | 12103402 | 40      | not necessary      |
| Caelo    | Galangal root        | 14159504 | 60      | 1511617            |
| Caelo    | Galangal root        | 11375909 | 40      | 1403324            |
| Caelo    | Galangal root        | 12330308 | 40      | not necessary      |
| Caelo    | Galangal root        | 11375904 | 40      | not necessary      |
| Caelo    | Galangal root        | 11048908 | 40      | not necessary      |
| Caelo    | Galangal root        | 11196506 | 40      | pending            |
| Caelo    | Galangal root        | 12125001 | 40      | not necessary      |
| Caelo    | Galangal root        | 12330305 | 40      | 1403491            |
| Caelo    | Garden violet, cut   | 08061209 | 40      | not necessary      |

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| Supplier | Substance           | Batch    | Spectra | Certificate        |
|----------|---------------------|----------|---------|--------------------|
| Caelo    | Garden violet, cut  | 10292002 | 40      | pending            |
| Caelo    | Garden violet, cut  | 13038703 | 40      | 1403481            |
| Caelo    | Garden violet, cut  | 13232103 | 40      | not necessary      |
| Caelo    | Gentian root, cut   | 12244603 | 40      | not necessary      |
| Caelo    | Gentian root, cut   | 10263402 | 40      | not necessary      |
| Caelo    | Gentian root, cut   | 10263402 | 40      | AR-12-FG-007932-01 |
| Caelo    | Gentian root, po... | 09130203 | 50      | not necessary      |
| Caelo    | Gentian root, po... | 12007106 | 40      | not necessary      |
| Caelo    | Gentian root, po... | 13410503 | 40      | 1508394            |
| Caelo    | Gentian root, po... | 12007103 | 50      | 1403630            |
| Caelo    | Ginger, peeled      | 13321904 | 40      | not necessary      |
| Caelo    | Ginger, peeled      | 11325715 | 40      | not necessary      |
| Caelo    | Ginger, peeled      | 14120701 | 40      | not necessary      |
| Caelo    | Ginger, peeled      | 12180601 | 40      | not necessary      |
| Caelo    | Ginkgo extract      | 12192505 | 40      | 1403672            |
| Caelo    | Ginkgo leaf, cut    | 16281501 | 60      | 1708047            |
| Caelo    | Ginkgo leaf, cut    | 13340907 | 60      | not necessary      |
| Caelo    | Ginkgo leaf, cut    | 12151703 | 40      | not necessary      |
| Caelo    | Ginkgo leaf, cut    | 12151703 | 40      | 1403707            |
| Caelo    | Ginkgo leaf, cut    | 13340904 | 40      | 1411088            |
| Caelo    | Ginseng root        | 13237805 | 40      | not necessary      |
| Caelo    | Ginseng root        | 11349206 | 30      | not necessary      |
| Caelo    | Ginseng root        | 12080208 | 40      | not necessary      |
| Caelo    | Ginseng root        | 13341008 | 40      | not necessary      |
| Caelo    | Goat's rue, cut     | 11175104 | 40      | not necessary      |
| Caelo    | Goat's rue, cut     | 11307903 | 40      | not necessary      |
| Caelo    | Goat's rue, cut     | 10022115 | 60      | not necessary      |
| Caelo    | Ground ivy herb,... | 10227602 | 40      | AR-12-FG-008589-01 |
| Caelo    | Guaiacum wood, cut  | 11352012 | 40      | not necessary      |
| Caelo    | Guaiacum wood, cut  | 13343802 | 40      | not necessary      |
| Caelo    | Guaiacum wood, cut  | 10143017 | 40      | not necessary      |
| Caelo    | Guaiacum wood, cut  | 11352001 | 40      | 1406340            |
| Caelo    | Hamamelis bark, ... | pending  | 40      | not necessary      |
| Caelo    | Hamamelis bark, ... | 12361301 | 40      | not necessary      |
| Caelo    | Hamamelis bark, ... | 10140405 | 40      | not necessary      |
| Caelo    | Hamamelis bark, ... | 12361303 | 40      | not necessary      |
| Caelo    | Hamamelis leaf, ... | 10102915 | 40      | not necessary      |
| Caelo    | Hamamelis leaf, ... | 10102915 | 40      | not necessary      |
| Caelo    | Hamamelis leaf, ... | 13269904 | 40      | not necessary      |
| Caelo    | Hamamelis leaf, ... | 13269902 | 40      | 1405176            |
| Caelo    | Hamamelis leaf, ... | pending  | 40      | not necessary      |
| Caelo    | Hawthorn flower     | 13010403 | 40      | not necessary      |
| Caelo    | Hawthorn flower     | 10157201 | 40      | not necessary      |
| Caelo    | Hawthorn flower     | 10157201 | 80      | not necessary      |
| Caelo    | Hawthorn fruit      | 11278205 | 40      | not necessary      |
| Caelo    | Hawthorn fruit      | 11183003 | 40      | not necessary      |
| Caelo    | Hawthorn fruit      | 11183010 | 40      | not necessary      |
| Caelo    | Hawthorn fruit      | 11278203 | 40      | not necessary      |
| Caelo    | Hawthorn leaf wi... | 10273515 | 40      | not necessary      |
| Caelo    | Hawthorn leaf wi... | 09363904 | 40      | not necessary      |
| Caelo    | Hawthorn leaf wi... | 10273507 | 40      | AR-12-FG-008080-01 |
| Caelo    | Hawthorn leaf wi... | 13276706 | 40      | not necessary      |
| Caelo    | Hawthorn leaf wi... | 10377902 | 50      | not necessary      |
| Caelo    | Hawthorn leaf wi... | 10273513 | 40      | not necessary      |
| Caelo    | Hay flower          | 82612379 | 80      | F 2009 001 015     |
| Caelo    | Hay flower          | 12317104 | 40      | not necessary      |
| Caelo    | Heather flower, ... | 10270508 | 40      | not necessary      |
| Caelo    | Heather, cut        | 09291512 | 40      | not necessary      |
| Caelo    | Heather, cut        | 11011209 | 40      | not necessary      |
| Caelo    | Heavy alkaline b... | 11052805 | 40      | not necessary      |

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| Supplier | Substance           | Batch    | Spectra | Certificate        |
|----------|---------------------|----------|---------|--------------------|
| Caelo    | Heavy, basic mag... | 10290208 | 40      | not necessary      |
| Caelo    | Henna powder        | 12122302 | 30      | from supplier      |
| Caelo    | Henna powder        | 13298604 | 40      | not necessary      |
| Caelo    | Henna powder        | 13262801 | 40      | not necessary      |
| Caelo    | Henna powder        | 11048703 | 40      | from supplier      |
| Caelo    | Henna powder        | 10220907 | 40      | from supplier      |
| Caelo    | Henna powder        | 12267304 | 30      | from supplier      |
| Caelo    | Hop strobile        | 12221802 | 40      | not necessary      |
| Caelo    | Hop strobile        | 12008305 | 40      | not necessary      |
| Caelo    | Hop strobile        | 12008305 | 40      | not necessary      |
| Caelo    | Hop strobile        | 10240317 | 40      | not necessary      |
| Caelo    | Hop strobile        | 82463349 | 80      | F 2009 001 080     |
| Caelo    | Horse chestnut l... | 83418159 | 70      | F 2010 000 048     |
| Caelo    | Horse chestnut l... | 11063503 | 40      | not necessary      |
| Caelo    | Hydromorphone hy... | 15393602 | 20      | 1516J-01334        |
| Caelo    | Hydromorphone hy... | 16123804 | 40      | 1917R-01334        |
| Caelo    | Hydromorphone hy... | 13267702 | 20      | 0914A-01334        |
| Caelo    | Hydromorphone hy... | 16123804 | 40      | 1917R-01334        |
| Caelo    | Hydromorphone hy... | 11029713 | 40      | not necessary      |
| Caelo    | Hydromorphone hy... | 15393602 | 20      | 1516J-01334        |
| Caelo    | Hydromorphone hy... | 10157908 | 80      | not necessary      |
| Caelo    | Hyssop herb, cut    | 11040908 | 40      | not necessary      |
| Caelo    | Iceland moss, cut   | 12187106 | 40      | 1403493            |
| Caelo    | Iceland moss, cut   | 09355507 | 40      | not necessary      |
| Caelo    | Iceland moss, cut   | 13350803 | 40      | not necessary      |
| Caelo    | Iodine              | 10237809 | 40      | not necessary      |
| Caelo    | Iron (II) sulfat... | 11340509 | 40      | 1401568            |
| Caelo    | Iron (III) chlor... | 12354703 | 40      | 1401391            |
| Caelo    | Isomalt             | 170812   | 40      | 20170421*          |
| Caelo    | Ispaghula husk      | 12148103 | 40      | not necessary      |
| Caelo    | Ispaghula husk      | 13238005 | 40      | not necessary      |
| Caelo    | Ispaghula seed      | 11185807 | 40      | not necessary      |
| Caelo    | Ispaghula seed      | 11185812 | 40      | not necessary      |
| Caelo    | Ivy leaf, cut       | 13276304 | 40      | not necessary      |
| Caelo    | Ivy leaf, cut       | 09355008 | 40      | AR-12-FG-008538-01 |
| Caelo    | Ivy leaf, cut       | 11229505 | 40      | not necessary      |
| Caelo    | Ivy leaf, cut       | 11101106 | 40      | not necessary      |
| Caelo    | Jasmine flower      | 12143201 | 40      | not necessary      |
| Caelo    | Java tea, cut       | 10184709 | 40      | AR-12-FG-008079-01 |
| Caelo    | Java tea, cut       | 12225702 | 40      | not necessary      |
| Caelo    | Java tea, cut       | 13258805 | 40      | not necessary      |
| Caelo    | Juniper             | 13267210 | 40      | not necessary      |
| Caelo    | Juniper             | 12028609 | 40      | not necessary      |
| Caelo    | Juniper             | 10311601 | 50      | not necessary      |
| Caelo    | Juniper, pounded    | 12278903 | 40      | 1405296            |
| Caelo    | Juniper, pounded    | 13367302 | 40      | not necessary      |
| Caelo    | Juniper, pounded    | 12113701 | 40      | not necessary      |
| Caelo    | Juniper, powdered   | 05031207 | 40      | not necessary      |
| Caelo    | Kaolin, heavy       | 11350124 | 40      | not necessary      |
| Caelo    | Kaolin, heavy       | 82043269 | 40      | from supplier      |
| Caelo    | Kaolin, red, pow... | 12093503 | 40      | from supplier      |
| Caelo    | Kelp, cut           | 13230805 | 40      | AR-15-FG-007678-01 |
| Caelo    | Kelp, cut           | 15418801 | 60      | AR-17-FG-007505-01 |
| Caelo    | Kelp, cut           | 11351105 | 40      | pending            |
| Caelo    | Kidney vetch, co... | 10249206 | 40      | not necessary      |
| Caelo    | Knotgrass, cut      | 11369301 | 40      | not necessary      |
| Caelo    | Knotgrass, cut      | pending  | 40      | not necessary      |
| Caelo    | Knotgrass, cut      | 14079304 | 40      | not necessary      |
| Caelo    | Knotgrass, cut      | 11369702 | 40      | not necessary      |
| Caelo    | Ladys bedstraw ...  | 11265103 | 40      | not necessary      |

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| Supplier | Substance            | Batch    | Spectra | Certificate        |
|----------|----------------------|----------|---------|--------------------|
| Caelo    | Ladys bedstraw ...   | 82879439 | 70      | F 2010 000 060     |
| Caelo    | Lapacho wood, cut    | 12239305 | 40      | not necessary      |
| Caelo    | Lapacho wood, cut    | 11154503 | 40      | 1403811            |
| Caelo    | Large waybread h...  | 10349610 | 40      | not necessary      |
| Caelo    | Laurel leaf          | 12299103 | 40      | not necessary      |
| Caelo    | Laurel leaf          | 11223607 | 40      | not necessary      |
| Caelo    | Laurel leaf          | 11223609 | 40      | not necessary      |
| Caelo    | Lavender flower      | 10144302 | 40      | AR-12-FG-003625-01 |
| Caelo    | Lavender flower      | 12088003 | 60      | not necessary      |
| Caelo    | Lavender flower      | 11327903 | 40      | not necessary      |
| Caelo    | Lavender flower      | 13336005 | 40      | from supplier      |
| Caelo    | Lemon grass, cut     | 11301503 | 40      | not necessary      |
| Caelo    | Lemon peel, cut      | pending  | 40      | not necessary      |
| Caelo    | Lemon peel, cut      | 12217402 | 40      | not necessary      |
| Caelo    | Lemon verbena le...  | 12137503 | 40      | not necessary      |
| Caelo    | Lemon verbena le...  | 12137505 | 40      | not necessary      |
| Caelo    | Lime flower, cut     | 91680399 | 70      | F 2009 001 020     |
| Caelo    | Lime flower, cut     | 11086305 | 55      | not necessary      |
| Caelo    | Linseed              | 91729389 | 70      | F 2010 000 069     |
| Caelo    | Linseed              | 13296703 | 40      | not necessary      |
| Caelo    | Linseed              | 12092102 | 60      | not necessary      |
| Caelo    | Linseed              | 13412801 | 40      | not necessary      |
| Caelo    | Linseed              | 12186902 | 60      | pending            |
| Caelo    | Liquorice root, ...  | 12227106 | 40      | not necessary      |
| Caelo    | Liquorice root, ...  | 11351911 | 40      | not necessary      |
| Caelo    | Liquorice root, ...  | 90659329 | 70      | F 2009 001 062     |
| Caelo    | Liquorice root, ...  | 11002811 | 40      | AR-13-FG-000112-01 |
| Caelo    | Liquorice root, ...  | 12227101 | 40      | not necessary      |
| Caelo    | Liquorice            | 13262501 | 40      | pending            |
| Caelo    | Liquorice            | 13180904 | 60      | pending            |
| Caelo    | Liquorice            | 13068904 | 40      | not necessary      |
| Caelo    | Liquorice            | 11267801 | 40      | pending            |
| Caelo    | Liquorice            | 14050601 | 25      | not necessary      |
| Caelo    | Liquorice root, ...  | 12267103 | 40      | not necessary      |
| Caelo    | Locust bean gum,...  | 13379403 | 40      | from supplier      |
| Caelo    | Locust bean gum,...  | 10376516 | 40      | not necessary      |
| Caelo    | Lovage root, cut     | 10249312 | 30      | not necessary      |
| Caelo    | Lovage root, cut     | 11181609 | 40      | not necessary      |
| Caelo    | Lungwort herb, cut   | 11021701 | 40      | not necessary      |
| Caelo    | Lycopodium herb,...  | 73075379 | 60      | F 2009 001 051     |
| Caelo    | Mace, powdered (...) | 14256901 | 60      | pending            |
| Caelo    | Mace, powdered (...) | 13132201 | 40      | not necessary      |
| Caelo    | Mace, powdered (...) | 13132204 | 40      | pending            |
| Caelo    | Mace, powdered (...) | 14256901 | 60      | not necessary      |
| Caelo    | Magensium hydrog...  | 12181911 | 40      | not necessary      |
| Caelo    | Magnesium chlori...  | 11345606 | 40      | AR-13-FG-005982-01 |
| Caelo    | Magnesium chlori...  | 11032316 | 40      | not necessary      |
| Caelo    | Magnesium chlori...  | 11218705 | 40      | AR-12-FG-007022-01 |
| Caelo    | Magnesium chlori...  | 11032304 | 50      | not necessary      |
| Caelo    | Magnesium chlori...  | 10043911 | 40      | not necessary      |
| Caelo    | Magnesium hydrox...  | 16253301 | 40      | not necessary      |
| Caelo    | Magnesium sulfat...  | 11231006 | 40      | AR-12-FG-007046-01 |
| Caelo    | Magnesium sulfat...  | 13340814 | 60      | not necessary      |
| Caelo    | Magnesium sulfat...  | 09246402 | 40      | not necessary      |
| Caelo    | Magnesium sulfat...  | 09377510 | 40      | not necessary      |
| Caelo    | Maize style, cut     | 09074201 | 70      | F 2009 001 078     |
| Caelo    | Maize style, cut     | 13381501 | 40      | not necessary      |
| Caelo    | Maize style, cut     | 10325902 | 40      | not necessary      |
| Caelo    | Maize style, cut     | 10325906 | 40      | not necessary      |
| Caelo    | Male speedwell w...  | 12162503 | 40      | not necessary      |

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| Supplier | Substance           | Batch    | Spectra | Certificate        |
|----------|---------------------|----------|---------|--------------------|
| Caelo    | Male speedwell w... | 11265502 | 40      | AR-12-FG-008537-01 |
| Caelo    | Male speedwell w... | 11265501 | 40      | not necessary      |
| Caelo    | Mallow flower, cut  | 12187405 | 40      | not necessary      |
| Caelo    | Mallow flower, cut  | 09311103 | 50      | not necessary      |
| Caelo    | Mallow flower, cut  | 09311103 | 69      | F 2010 000 045     |
| Caelo    | Mallow leaf, cut    | 12153403 | 40      | not necessary      |
| Caelo    | Mallow leaf, cut    | 10290507 | 50      | not necessary      |
| Caelo    | Mallow leaf, cut    | 10054507 | 40      | from supplier      |
| Caelo    | Manganese sulfat... | 91547399 | 40      | AR-13-FG-000299-01 |
| Caelo    | Manna, cut          | 13127007 | 40      | pending            |
| Caelo    | Manna, cut          | 82063319 | 80      | F 2010 000 064     |
| Caelo    | Manna, cut          | 11308907 | 60      | pending            |
| Caelo    | Manna, powdered     | 14001401 | 40      | not necessary      |
| Caelo    | Manna, powdered     | 11308807 | 40      | 1403534            |
| Caelo    | Manna, powdered     | 11003608 | 40      | not necessary      |
| Caelo    | Marian thistle f... | 11126703 | 40      | not necessary      |
| Caelo    | Marian thistle f... | 13342002 | 40      | from supplier      |
| Caelo    | Marian thistle f... | 10270610 | 40      | not necessary      |
| Caelo    | Marian thistle f... | 90494349 | 70      | F 2009 001 039     |
| Caelo    | Marian thistle h... | 10365601 | 40      | not necessary      |
| Caelo    | Marian thistle h... | 10315902 | 40      | AR-12-FG-008389-01 |
| Caelo    | Marian thistle h... | 10365601 | 40      | not necessary      |
| Caelo    | Marian thistle h... | 10326301 | 40      | not necessary      |
| Caelo    | Marjoram herb, r... | 90319439 | 70      | F 2009 001 052     |
| Caelo    | Marrubium vulgar... | 11073110 | 40      | not necessary      |
| Caelo    | Marshmallow leaf... | 11101007 | 40      | not necessary      |
| Caelo    | Marshmallow leaf... | 11100902 | 40      | AR-12-FG-008596-01 |
| Caelo    | Marshmallow leaf... | 12328206 | 40      | not necessary      |
| Caelo    | Marshmallow leaf... | 11101005 | 40      | not necessary      |
| Caelo    | Marshmallow root... | 11101905 | 40      | not necessary      |
| Caelo    | Marshmallow root... | 13214804 | 40      | not necessary      |
| Caelo    | Marshmallow root... | 81892149 | 80      | F 2009 001 058     |
| Caelo    | Masterwort root,... | 12101804 | 60      | not necessary      |
| Caelo    | Masterwort root,... | 12101801 | 40      | not necessary      |
| Caelo    | Masterwort root,... | 13341204 | 40      | not necessary      |
| Caelo    | Maté leaf, cut      | 10126408 | 40      | not necessary      |
| Caelo    | Maté leaf, cut      | 11091707 | 40      | not necessary      |
| Caelo    | Maté leaf, cut      | 13118004 | 40      | not necessary      |
| Caelo    | Maté leaf, cut      | 11091707 | 40      | not necessary      |
| Caelo    | Matricaria flower   | 91357379 | 70      | F 2010 000 044     |
| Caelo    | Matricaria flower   | 10014213 | 39      | not necessary      |
| Caelo    | Matricaria flower   | 12294804 | 40      | not necessary      |
| Caelo    | Matricaria flower   | 12337605 | 40      | not necessary      |
| Caelo    | Matricaria flower   | 11255204 | 80      | not necessary      |
| Caelo    | Matricaria flower   | 11214806 | 40      | not necessary      |
| Caelo    | Matricaria flowe... | 12115805 | 40      | not necessary      |
| Caelo    | Meadowsweet flow... | 08223003 | 70      | F 2010 000 047     |
| Caelo    | Meadowsweet flow... | 12275701 | 40      | not necessary      |
| Caelo    | Meadowsweet herb... | 09171501 | 80      | F 2009 001 054     |
| Caelo    | Melilot herb, cut   | 83011399 | 70      | F 2010 000 062     |
| Caelo    | Melissa leaf, cut   | 90984399 | 100     | F 2009 001 023     |
| Caelo    | Melissa leaf, cut   | 12032318 | 40      | not necessary      |
| Caelo    | Melissa leaf, cut   | 10310911 | 30      | not necessary      |
| Caelo    | Melissa leaf, cut   | 13214713 | 40      | not necessary      |
| Caelo    | Methadone hydroc... | 11043910 | 40      | not necessary      |
| Caelo    | Methadone hydroc... | 15244715 | 20      | 1516A-02949        |
| Caelo    | Methadone hydroc... | 12344818 | 20      | 0914E-02949        |
| Caelo    | Methadone hydroc... | 16135309 | 40      | 1917R-02949        |
| Caelo    | Methadone hydroc... | 16135309 | 40      | 1917R-02949        |
| Caelo    | Methadone hydroc... | 15244715 | 20      | 1516A-02949        |

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| Supplier | Substance           | Batch    | Spectra | Certificate        |
|----------|---------------------|----------|---------|--------------------|
| Caelo    | Methylrosanilini... | 12276308 | 40      | 1509299            |
| Caelo    | Midazolam hydroc... | 15224611 | 30      | 1917S-03538        |
| Caelo    | Midazolam hydroc... | 12215811 | 20      | 0914E-03538        |
| Caelo    | Midazolam hydroc... | 15224611 | 40      | 1917S-03538        |
| Caelo    | Midazolam hydroc... | 15224602 | 20      | 1516B-03538        |
| Caelo    | Midazolam hydroc... | 11184701 | 40      | not necessary      |
| Caelo    | Midazolam hydroc... | 15224602 | 20      | 1516B-03538        |
| Caelo    | Mistletoe, cut      | 11294003 | 40      | not necessary      |
| Caelo    | Mistletoe, cut      | 08189101 | 70      | F 2009 001 056     |
| Caelo    | Molecular distil... | 11160012 | 40      | not necessary      |
| Caelo    | Morphine hydroch... | 15439404 | 20      | 1416R-01879        |
| Caelo    | Morphine hydroch... | 13349505 | 20      | 0914F-01879        |
| Caelo    | Morphine hydroch... | 16184605 | 40      | 1917S-01879        |
| Caelo    | Morphine hydroch... | 15439404 | 20      | 1416R-01879        |
| Caelo    | Morphine hydroch... | 15439411 | 40      | 1917R-01879        |
| Caelo    | Morphine hydroch... | 13125207 | 20      | 0914E-01879        |
| Caelo    | Morphine hydroch... | 15439411 | 40      | 1917R-01879        |
| Caelo    | Morphine sulfate    | 15295802 | 40      | 1917R-07776        |
| Caelo    | Morphine sulfate    | 11333103 | 20      | 0914E-07776        |
| Caelo    | Morphine sulfate    | 15255703 | 20      | 1416Q-07776        |
| Caelo    | Morphine sulfate    | 15255703 | 20      | 1416Q-07776        |
| Caelo    | Morphine sulfate    | 15295802 | 40      | 1917R-07776        |
| Caelo    | Morphine sulfate    | 12153212 | 60      | 0914F-07776        |
| Caelo    | Motherwort herb,... | pending  | 40      | not necessary      |
| Caelo    | Motherwort herb,... | 09336508 | 40      | AR-12-FG-008693-01 |
| Caelo    | Motherwort herb,... | 10244612 | 40      | not necessary      |
| Caelo    | Mullein flower      | 11366403 | 40      | not necessary      |
| Caelo    | Mullein flower, ... | 91937409 | 70      | F 2009 001 021     |
| Caelo    | Mullein flower, ... | 11233402 | 60      | not necessary      |
| Caelo    | Myrrh               | 10057904 | 40      | pending            |
| Caelo    | Myrrh               | 11277111 | 60      | 1403081            |
| Caelo    | Myrrh               | 13108701 | 40      | AR-15-FG-000946-01 |
| Caelo    | Myrrh               | 12269901 | 40      | 1403470            |
| Caelo    | Nettle leaf, cut    | 10161802 | 50      | not necessary      |
| Caelo    | Nettle leaf, cut    | 12184702 | 40      | not necessary      |
| Caelo    | Nettle leaf, cut    | 83142389 | 79      | F 2009 001 027     |
| Caelo    | Nettle root, cut    | 11254903 | 40      | not necessary      |
| Caelo    | Nettle root, cut    | 11254903 | 40      | not necessary      |
| Caelo    | Nettle seed         | 12131507 | 40      | 1402203            |
| Caelo    | Nettle seed         | 11126211 | 40      | pending            |
| Caelo    | Nettle seed         | 11126212 | 40      | not necessary      |
| Caelo    | Nettle seed         | 13387110 | 40      | 1410300            |
| Caelo    | Nutmeg              | 12067304 | 40      | not necessary      |
| Caelo    | Nutmeg              | 13266002 | 40      | not necessary      |
| Caelo    | Nutmeg, powdered... | 10085809 | 50      | pending            |
| Caelo    | Nutmeg, powdered... | 13097204 | 40      | 1403540            |
| Caelo    | Nystatin            | 11069721 | 40      | not necessary      |
| Caelo    | Nystatin            | 10280622 | 30      | not necessary      |
| Caelo    | Oak bark, cut       | 10348603 | 40      | not necessary      |
| Caelo    | Oak bark, cut       | 09357416 | 30      | not necessary      |
| Caelo    | Oak bark, cut       | 13360306 | 40      | not necessary      |
| Caelo    | Oak bark, cut       | 10348617 | 40      | not necessary      |
| Caelo    | Oak bark, cut       | 11351207 | 40      | 1403492            |
| Caelo    | Oak bark, powdered  | 11235004 | 40      | not necessary      |
| Caelo    | Oat straw, cut      | 10092003 | 30      | not necessary      |
| Caelo    | Oat straw, cut      | 11280008 | 40      | not necessary      |
| Caelo    | Olive leaf          | 12316808 | 60      | AR-15-FG-001051-01 |
| Caelo    | Olive leaf          | 11270106 | 40      | not necessary      |
| Caelo    | Oregano herb        | 11340703 | 40      | not necessary      |
| Caelo    | Orris root          | 12206802 | 40      | not necessary      |

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| Supplier | Substance           | Batch    | Spectra | Certificate        |
|----------|---------------------|----------|---------|--------------------|
| Caelo    | Orris root          | 12206701 | 40      | not necessary      |
| Caelo    | Orris root          | 11026705 | 40      | not necessary      |
| Caelo    | Orris root          | 11026702 | 40      | not necessary      |
| Caelo    | Oxetacaine          | 172498   | 40      | 20190925*          |
| Caelo    | Oxycodone hydroc... | 12268908 | 20      | 0914E-07734        |
| Caelo    | Oxycodone hydroc... | 09190426 | 40      | not necessary      |
| Caelo    | Oxycodone hydroc... | 12268914 | 20      | 1416Q-07734        |
| Caelo    | Oxycodone hydroc... | 12268914 | 20      | 1416Q-07734        |
| Caelo    | Oxycodone hydroc... | 12268913 | 20      | 1416R-07734        |
| Caelo    | Oxycodone hydroc... | 15220205 | 40      | 2017A-07734        |
| Caelo    | Oxycodone hydroc... | 12268913 | 20      | 1416R-07734        |
| Caelo    | Oxycodone hydroc... | 15220205 | 40      | 2017A-07734        |
| Caelo    | Oxycodone hydroc... | 12034515 | 20      | 0914F-07734        |
| Caelo    | Parsley herb, ru... | 10269904 | 40      | not necessary      |
| Caelo    | Parsley herb, ru... | 10269904 | 40      | not necessary      |
| Caelo    | Parsley root, cut   | 12080301 | 40      | not necessary      |
| Caelo    | Parsley root, cut   | pending  | 40      | not necessary      |
| Caelo    | Parsley root, cut   | 10134905 | 50      | not necessary      |
| Caelo    | Parsley seed        | 11157810 | 40      | pending            |
| Caelo    | Passionflower he... | 10079510 | 40      | not necessary      |
| Caelo    | Peppermint leaf,... | 11294411 | 40      | not necessary      |
| Caelo    | Peppermint leaf,... | 11294401 | 40      | not necessary      |
| Caelo    | Peppermint leaf,... | 12321503 | 130     | not necessary      |
| Caelo    | Peppermint leaf,... | 10199902 | 40      | not necessary      |
| Caelo    | Peppermint leaf,... | 91321429 | 140     | F 2010 000 049     |
| Caelo    | Peppermint leaf,... | 13288303 | 40      | not necessary      |
| Caelo    | Peppermint leaf,... | 11347607 | 40      | not necessary      |
| Caelo    | Phenobarbital       | 11045503 | 40      | not necessary      |
| Caelo    | Phenobarbital       | 12173202 | 20      | 0914E-01040        |
| Caelo    | Phenol              | 11163809 | 50      | not necessary      |
| Caelo    | Pine sprouts, cut   | 13256105 | 40      | not necessary      |
| Caelo    | Pine sprouts, cut   | 11164708 | 60      | not necessary      |
| Caelo    | Piper cubeba        | 11081903 | 40      | not necessary      |
| Caelo    | Podophyllum resi... | 09315906 | 50      | not necessary      |
| Caelo    | Podophyllum resi... | 12287810 | 40      | 1405242            |
| Caelo    | Potassium bromide   | 11208211 | 27      | not necessary      |
| Caelo    | Potassium carbon... | 09302910 | 40      | not necessary      |
| Caelo    | Potassium hydroc... | 10052616 | 40      | AR-12-FG-002698-01 |
| Caelo    | Potassium hydroc... | 10052622 | 50      | not necessary      |
| Caelo    | Potassium hydrog... | 11005709 | 10      | not necessary      |
| Caelo    | Potassium hydrog... | 172493   | 40      | 20170911*          |
| Caelo    | Potassium hydrox... | 10042008 | 40      | not necessary      |
| Caelo    | Potassium monohy... | 12366501 | 40      | 10401307           |
| Caelo    | Potassium monohy... | 71045347 | 40      | not necessary      |
| Caelo    | Potassium perman... | 10283104 | 35      | not necessary      |
| Caelo    | Primrose flower     | 10072509 | 40      | not necessary      |
| Caelo    | Primrose flower     | 11268002 | 40      | not necessary      |
| Caelo    | Primrose flower     | 11206806 | 100     | not necessary      |
| Caelo    | Primrose flower     | 82709399 | 89      | F 2009 001 018     |
| Caelo    | Primrose root, cut  | 12064506 | 40      | not necessary      |
| Caelo    | Primrose root, cut  | 10382013 | 40      | not necessary      |
| Caelo    | Propolis extract... | 11124120 | 40      | 1403460            |
| Caelo    | Propolis extract... | 13396103 | 40      | not necessary      |
| Caelo    | Propolis extract... | 13396103 | 40      | not necessary      |
| Caelo    | Psyllium seed       | 91730289 | 70      | F 2009 001 077     |
| Caelo    | Psyllium seed       | 10291205 | 80      | not necessary      |
| Caelo    | Psyllium seed       | 13305903 | 40      | pending            |
| Caelo    | Psyllium seed       | 10291206 | 40      | pending            |
| Caelo    | Pumpkin seed, pe... | 12249002 | 40      | 1404542            |
| Caelo    | Pumpkin seed, pe... | 12249006 | 40      | not necessary      |

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| Supplier | Substance           | Batch    | Spectra | Certificate    |
|----------|---------------------|----------|---------|----------------|
| Caelo    | Ramsons herb, cut   | 12380801 | 40      | 1404538        |
| Caelo    | Ramsons herb, cut   | 13072801 | 40      | not necessary  |
| Caelo    | Ramsons herb, cut   | 11182205 | 40      | pending        |
| Caelo    | Raspberry leaf, ... | 09052715 | 50      | not necessary  |
| Caelo    | Raspberry leaf, ... | 09052710 | 40      | not necessary  |
| Caelo    | Raspberry leaf, ... | 12362701 | 40      | not necessary  |
| Caelo    | Raspberry leaf, ... | 83211409 | 70      | F 2009 001 025 |
| Caelo    | Red poppy petals... | 12008104 | 40      | not necessary  |
| Caelo    | Red-rose petal      | 11299204 | 40      | not necessary  |
| Caelo    | Red-rose petal, ... | 09184902 | 70      | F 2010 000 046 |
| Caelo    | Red-rose petal, ... | 11304912 | 40      | not necessary  |
| Caelo    | Redwood             | 12049603 | 40      | 1403471        |
| Caelo    | Redwood             | 12049604 | 40      | not necessary  |
| Caelo    | Restharrow root,... | 91697439 | 69      | F 2010 000 066 |
| Caelo    | Restharrow root,... | 12330001 | 40      | not necessary  |
| Caelo    | Rhubarb, cut        | 11057818 | 40      | not necessary  |
| Caelo    | Rhubarb, cut        | 13235213 | 40      | not necessary  |
| Caelo    | Rhubarb, cut        | 12211906 | 40      | not necessary  |
| Caelo    | Rhubarb, cut        | 09213604 | 40      | not necessary  |
| Caelo    | Rhubarb, cut        | 11057818 | 40      | not necessary  |
| Caelo    | Rhubarb, powdered   | 10162405 | 50      | not necessary  |
| Caelo    | Rhubarb, powdered   | 11043818 | 60      | 1403280        |
| Caelo    | Rhubarb, powdered   | 16009901 | 26      | 9886           |
| Caelo    | Ribwort plantain... | 09297505 | 40      | not necessary  |
| Caelo    | Ribwort plantain... | 10315703 | 40      | not necessary  |
| Caelo    | Ribwort plantain... | 10328701 | 40      | not necessary  |
| Caelo    | Ribwort plantain... | 12362902 | 40      | not necessary  |
| Caelo    | Ribwort plantain... | 10315701 | 50      | not necessary  |
| Caelo    | Ribwort plantain... | 82678059 | 60      | F 2009 001 024 |
| Caelo    | Rifaximin           | 161053   | 60      | 20160607*      |
| Caelo    | Robert herb, cut    | 10008504 | 40      | not necessary  |
| Caelo    | Rose hips peel, ... | 11301407 | 60      | not necessary  |
| Caelo    | Rose hips peel, ... | 11301403 | 40      | not necessary  |
| Caelo    | Rose hips peel, ... | 90907504 | 73      | from supplier  |
| Caelo    | Rose hips with p... | 12029002 | 40      | not necessary  |
| Caelo    | Rose hips with p... | 09354513 | 40      | not necessary  |
| Caelo    | Rose hips with p... | 11232204 | 40      | not necessary  |
| Caelo    | Rose hips with p... | 12064202 | 40      | not necessary  |
| Caelo    | Rose mallow flow... | 10244508 | 60      | not necessary  |
| Caelo    | Rose mallow flow... | 82462399 | 70      | F 2009 001 017 |
| Caelo    | Roselle             | 12007311 | 60      | not necessary  |
| Caelo    | Roselle             | 11036509 | 60      | not necessary  |
| Caelo    | Roselle             | 10008813 | 40      | not necessary  |
| Caelo    | Roselle             | 00266655 | 40      | from supplier  |
| Caelo    | Rosemary leaf, cut  | 09144202 | 80      | F 2010 000 051 |
| Caelo    | Rosemary leaf, cut  | 14159601 | 60      | not necessary  |
| Caelo    | Rosemary leaf, cut  | 10139805 | 40      | not necessary  |
| Caelo    | Rosemary leaf, cut  | 11193408 | 40      | not necessary  |
| Caelo    | Rue herb, cut       | 09336805 | 40      | not necessary  |
| Caelo    | Saffron (spice)     | 11293404 | 40      | not necessary  |
| Caelo    | Saffron filaments   | 10184819 | 40      | not necessary  |
| Caelo    | Sage leaf, cut      | 83091439 | 80      | F 2009 001 026 |
| Caelo    | Sage leaf, cut      | 11347503 | 40      | not necessary  |
| Caelo    | Sage leaf, cut      | 11056104 | 40      | not necessary  |
| Caelo    | Sarsaparilla roo... | 10230402 | 60      | not necessary  |
| Caelo    | Savory, rubbed      | 10375313 | 40      | not necessary  |
| Caelo    | Senna leaf, cut     | 90431299 | 80      | F 2010 000 052 |
| Caelo    | Senna leaf, cut     | 12273106 | 40      | not necessary  |
| Caelo    | Senna leaf, powd... | 11193307 | 120     | pending        |
| Caelo    | Senna leaf, powd... | 12369908 | 40      | 1408079        |

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| Supplier | Substance           | Batch     | Spectra | Certificate        |
|----------|---------------------|-----------|---------|--------------------|
| Caelo    | Senna pods, tinn... | 13395106  | 40      | not necessary      |
| Caelo    | Senna pods, tinn... | 12267605  | 40      | not necessary      |
| Caelo    | Senna pods, tinn... | 11154404  | 40      | not necessary      |
| Caelo    | Senna pods, tinn... | 10052013  | 39      | not necessary      |
| Caelo    | Sesame seed         | 12125201  | 40      | pending            |
| Caelo    | Sesame seed         | 12310205  | 40      | 1403406            |
| Caelo    | Shepherd's purse... | 81468389  | 70      | F 2009 001 044     |
| Caelo    | Shepherd's purse... | 11328208  | 40      | not necessary      |
| Caelo    | Shepherd's purse... | 11328204  | 40      | not necessary      |
| Caelo    | Siam benzoin        | 12321312  | 40      | pending            |
| Caelo    | Siam benzoin        | 12321314  | 40      | not necessary      |
| Caelo    | Silver nitrate      | 11027007  | 21      | not necessary      |
| Caelo    | Silverweed, cut     | 11016402  | 40      | not necessary      |
| Caelo    | Silverweed, cut     | 11328105  | 40      | not necessary      |
| Caelo    | Silverweed, cut     | 09362602  | 80      | not necessary      |
| Caelo    | Sodium bromide      | 10345710  | 40      | AR-13-FG-002996-01 |
| Caelo    | Sodium carbonate... | 10188901  | 40      | AR-13-FG-000310-01 |
| Caelo    | Sodium carbonate... | 16310205  | 30      | not necessary      |
| Caelo    | Sodium dihydroge... | 12198506  | 40      | not necessary      |
| Caelo    | Sodium hydrogen ... | 90962189  | 40      | not necessary      |
| Caelo    | Sodium iodide       | 161701    | 40      | 20160706*          |
| Caelo    | Sodium monohydro... | 08300209  | 40      | not necessary      |
| Caelo    | Sodium monohydro... | 12109002  | 40      | not necessary      |
| Caelo    | Sodium monohydro... | 10135302  | 36      | not necessary      |
| Caelo    | Sodium nitrate      | 11045910  | 40      | not necessary      |
| Caelo    | Sodium perborate... | 11158903  | 40      | not necessary      |
| Caelo    | Sodium sulfate d... | 11012210  | 40      | not necessary      |
| Caelo    | Sodium sulfate d... | 10044007  | 40      | not necessary      |
| Caelo    | Solanum dulcamar... | 09354613  | 40      | not necessary      |
| Caelo    | Solanum dulcamar... | 08154101  | 70      | F 2009 001 079     |
| Caelo    | Solanum dulcamar... | 13254305  | 40      | not necessary      |
| Caelo    | Solanum dulcamar... | 10375602  | 40      | not necessary      |
| Caelo    | Sorrel herb, cut    | pending   | 40      | not necessary      |
| Caelo    | Sour cherry stem... | 12042302  | 40      | 1503570            |
| Caelo    | Sour cherry stem... | 10367016  | 40      | 1402576            |
| Caelo    | Spearmint leaf, ... | 12133906  | 40      | not necessary      |
| Caelo    | Spearmint leaf, ... | pending   | 40      | not necessary      |
| Caelo    | St. John's wort,... | 73354159  | 70      | F 2010 000 061     |
| Caelo    | St. John's wort,... | 09297301  | 80      | not necessary      |
| Caelo    | Star anise          | 11314104  | 40      | not necessary      |
| Caelo    | Star anise          | 83439329  | 70      | F 2009 001 038     |
| Caelo    | Star anise, cut     | 15329302  | 60      | AR-16-FG-004770-01 |
| Caelo    | Star anise, cut     | 13041401  | 40      | 1403709            |
| Caelo    | Star anise, cut     | 12226301  | 60      | pending            |
| Caelo    | Stemless carline... | 11118001  | 40      | not necessary      |
| Caelo    | Stemless carline... | 12232802  | 40      | not necessary      |
| Caelo    | Stemless carline... | 12163702  | 40      | not necessary      |
| Caelo    | Stemless carline... | 91616279  | 76      | F 2009 001 061     |
| Caelo    | Strawberry leaf,... | 11117902  | 50      | not necessary      |
| Caelo    | Strawberry leaf,... | 11117903  | 40      | not necessary      |
| Caelo    | Sulfamerazine       | 10218403  | 40      | not necessary      |
| Caelo    | Sweet woodruff h... | 91789309  | 70      | F 2010 000 058     |
| Caelo    | Sweet woodruff h... | 10375812  | 30      | not necessary      |
| Caelo    | Talcum              | 10148813  | 40      | not necessary      |
| Caelo    | Talcum              | 11318312  | 120     | 1405338            |
| Caelo    | Tall golden rod,... | 11280306  | 40      | not necessary      |
| Caelo    | Tall golden rod,... | 09116601  | 80      | F 2009 001 053     |
| Caelo    | Tall golden rod,... | 11207014  | 40      | not necessary      |
| Caelo    | Tall nasturtium ... | 12031601  | 40      | not necessary      |
| Caelo    | Thea Nigra Ceylo... | CH0574162 | 60      | not necessary      |

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| Supplier | Substance           | Batch    | Spectra | Certificate        |
|----------|---------------------|----------|---------|--------------------|
| Caelo    | Thea Nigra Darje... | 0558812  | 40      | not necessary      |
| Caelo    | Thea Nigra Darje... | 0577101  | 40      | not necessary      |
| Caelo    | Theriac, powdered   | 11082412 | 40      | pending            |
| Caelo    | Theriac, powdered   | 13407301 | 40      | 1410336            |
| Caelo    | Theriac, powdered   | 12289307 | 40      | 1405122            |
| Caelo    | Theriac, powdered   | 10191904 | 50      | not necessary      |
| Caelo    | Thiomersal          | 172173   | 30      | 20170919*          |
| Caelo    | Thyme, rubbed       | 09016402 | 90      | F 2009 001 057     |
| Caelo    | Thyme, rubbed       | 11345004 | 60      | not necessary      |
| Caelo    | Tonka beans         | 12145101 | 40      | not necessary      |
| Caelo    | Tonka beans         | 12105101 | 40      | not necessary      |
| Caelo    | Tormentil           | 10290903 | 50      | not necessary      |
| Caelo    | Tormentil           | 12040708 | 40      | 1403487            |
| Caelo    | Tormentil           | 12013103 | 40      | 1403048            |
| Caelo    | Tormentil           | 12040715 | 40      | 1403710            |
| Caelo    | Tormentil           | 11102003 | 40      | pending            |
| Caelo    | Tormentil           | 13220502 | 40      | 1403049            |
| Caelo    | Tormentil           | 14360103 | 60      | 1606520            |
| Caelo    | Tormentil           | 10111704 | 50      | pending            |
| Caelo    | Tormentil           | 11102003 | 40      | pending            |
| Caelo    | Tragacanth, powd... | 15379906 | 60      | not necessary      |
| Caelo    | Tragacanth, powd... | 15085602 | 60      | not necessary      |
| Caelo    | Tragacanth, powd... | 13277804 | 60      | 1507149            |
| Caelo    | Tragacanth, powd... | 16110802 | 60      | AR-17-FG-007533-01 |
| Caelo    | Tragacanth, powd... | 09105901 | 30      | not necessary      |
| Caelo    | Trichloroacetic ... | 11294306 | 40      | AR-12-FG-004440-01 |
| Caelo    | Trichloroacetic ... | 81332099 | 20      | not necessary      |
| Caelo    | Turmeric root, cut  | 10162302 | 50      | not necessary      |
| Caelo    | Turmeric root, cut  | 12136503 | 40      | 1405295            |
| Caelo    | Turmeric root, cut  | 13360202 | 40      | 1411363            |
| Caelo    | Turmeric root, cut  | 11160403 | 60      | not necessary      |
| Caelo    | Turmeric, javane... | 12185605 | 40      | 1403465            |
| Caelo    | Turmeric, javane... | 13262904 | 40      | not necessary      |
| Caelo    | Turmeric, javane... | 11046305 | 50      | not necessary      |
| Caelo    | Turmeric, javane... | pending  | 40      | pending            |
| Caelo    | Turmeric, javane... | 12319206 | 40      | not necessary      |
| Caelo    | Valerian root, cut  | 90594289 | 80      | F 2009 001 063     |
| Caelo    | Valerian root, cut  | 12033809 | 40      | not necessary      |
| Caelo    | Valerian root, p... | 13113204 | 60      | pending            |
| Caelo    | Valerian root, p... | 12138008 | 40      | 1508496            |
| Caelo    | Valerian root, p... | 12138005 | 40      | 1403809            |
| Caelo    | Verbena herb, cut   | 90526329 | 70      | F 2009 001 055     |
| Caelo    | Verbena herb, cut   | 12187602 | 40      | not necessary      |
| Caelo    | Walnut bark, cut    | 11325603 | 40      | not necessary      |
| Caelo    | Walnut bark, cut    | 09269501 | 40      | not necessary      |
| Caelo    | Walnut leaf, cut    | 11103007 | 40      | 1403091            |
| Caelo    | Walnut leaf, cut    | 10050402 | 40      | not necessary      |
| Caelo    | Walnut leaf, cut    | 10050403 | 50      | not necessary      |
| Caelo    | White deadnettle... | 11371604 | 40      | not necessary      |
| Caelo    | White deadnettle... | 80213149 | 70      | F 2009 001 016     |
| Caelo    | White deadnettle... | 11010607 | 40      | not necessary      |
| Caelo    | White mustard seed  | 13064301 | 40      | pending            |
| Caelo    | White mustard seed  | 13380501 | 40      | not necessary      |
| Caelo    | White mustard seed  | 12361002 | 40      | 1403473            |
| Caelo    | White mustard se... | 12375705 | 40      | not necessary      |
| Caelo    | White mustard se... | 12349601 | 60      | 1403281            |
| Caelo    | White pepper        | 12294902 | 40      | 1403488            |
| Caelo    | White pepper        | 14010703 | 40      | not necessary      |
| Caelo    | White pepper        | 12294905 | 40      | not necessary      |
| Caelo    | Wild pansy, cut     | 10291007 | 60      | not necessary      |

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| Supplier         | Substance           | Batch          | Spectra | Certificate        |
|------------------|---------------------|----------------|---------|--------------------|
| Caelo            | Wild thyme, cut     | 11031207       | 40      | not necessary      |
| Caelo            | Wild thyme, cut     | pending        | 40      | not necessary      |
| Caelo            | Wild thyme, cut     | 11031204       | 39      | AR-13-FG-000087-01 |
| Caelo            | Willow bark, cut    | 11073210       | 40      | not necessary      |
| Caelo            | Willow bark, cut    | pending        | 40      | not necessary      |
| Caelo            | Willow bark, cut    | 12185204       | 40      | not necessary      |
| Caelo            | Willow herb, cut    | 91115419       | 70      | F 2009 001 047     |
| Caelo            | Willow herb, cut    | 11347311       | 40      | not necessary      |
| Caelo            | Willowherb, smal... | 10326106       | 40      | not necessary      |
| Caelo            | Willowherb, smal... | 73390419       | 70      | F 2009 001 046     |
| Caelo            | Willowherb, smal... | 09378909       | 40      | not necessary      |
| Caelo            | Willowherb, smal... | 13355904       | 60      | not necessary      |
| Caelo            | Willowherb, smal... | 10326104       | 40      | not necessary      |
| Caelo            | Willowherb, smal... | 10326106       | 40      | not necessary      |
| Caelo            | Wormwood herb, cut  | 11285811       | 40      | not necessary      |
| Caelo            | Wormwood herb, cut  | 09017102       | 70      | F 2010 000 056     |
| Caelo            | Wormwood herb, cut  | 12355801       | 40      | not necessary      |
| Caelo            | Yarrow flower, r... | 11106409       | 40      | not necessary      |
| Caelo            | Yarrow flower, r... | 12267703       | 40      | not necessary      |
| Caelo            | Yarrow flower, r... | 11106405       | 40      | not necessary      |
| Caelo            | Yarrow herb, cut    | 11280505       | 40      | not necessary      |
| Caelo            | Yarrow herb, cut    | 11218402       | 40      | AR-12-FG-008545-01 |
| Caelo            | Yarrow herb, cut    | 11280505       | 80      | not necessary      |
| Caelo            | Yarrow herb, cut    | 10076901       | 40      | not necessary      |
| Caelo            | Yarrow herb, cut    | 11280503       | 40      | not necessary      |
| Caelo            | Yarrow herb, cut    | 11092911       | 40      | not necessary      |
| Caelo            | Yarrow herb, cut    | 11092902       | 40      | not necessary      |
| Caelo            | Yarrow herb, cut    | 11092910       | 50      | not necessary      |
| Caelo            | Yarrow herb, cut    | pending        | 40      | not necessary      |
| Caelo            | Yarrow herb, cut    | 11218403       | 80      | not necessary      |
| Caelo            | Yarrow herb, cut    | 11280505       | 40      | not necessary      |
| Caelo            | Yellow brazil wo... | 12074804       | 40      | not necessary      |
| Caelo            | Yellow brazil wo... | 11336405       | 40      | not necessary      |
| Caelo            | Yellow brazil wo... | 12074803       | 40      | 1403479            |
| Caelo            | Yellow chaste we... | 11293101       | 40      | not necessary      |
| Caelo            | Yellow chaste we... | 10244407       | 40      | not necessary      |
| Caelo            | Yellow chaste we... | 10024611       | 40      | AR-12-FG-008692-01 |
| Caelo            | Zedoary root, cut   | 12125301       | 40      | not necessary      |
| Caelo            | Zedoary root, cut   | 82557319       | 80      | F 2009 001 076     |
| Caelo            | Zedoary root, cut   | 11091603       | 40      | not necessary      |
| Caelo            | Zedoary root, po... | 12344601       | 40      | 1403489            |
| Caelo            | Zedoary root, po... | 13165501       | 40      | pending            |
| Caelo            | Zedoary root, po... | 14249001       | 60      | not necessary      |
| Caelo            | Zinc chloride       | 11345504       | 40      | not necessary      |
| Caelo            | Zinc oxide          | 14038101       | 16      | not necessary      |
| Caelo            | Zinc oxide-talcu... | 10192202       | 40      | not necessary      |
| Caelo            | Zinc sulfate hep... | 12257802       | 40      | not necessary      |
| Caelo            | Zinc sulfate hep... | 11095602       | 40      | AR-13-FG-006298-01 |
| Carotech         | Tocomax 15%         | 100912         | 40      | from supplier      |
| Carotech         | Tocomax 20%         | A3_200003_1/5  | 40      | not necessary      |
| Denk             | Calcium aspartate   | N09814         | 40      | not necessary      |
| Denk             | s-adenosyl methi... | S1S1104B       | 20      | from supplier      |
| DKSH Switzerl... | Creatine            | 921831         | 30      | pending            |
| Dr. Behr         | Chlorella           | WE11070078     | 40      | pending            |
| Dr. Behr         | Chromium yeast 0... | WE-11040062    | 40      | not necessary      |
| Dr. Behr         | L-carnitine hydr... | 1520081202     | 40      | from supplier      |
| Dr. Behr         | L-carnitine hydr... | WE11030091     | 20      | from supplier      |
| Dr. Behr         | L-carnitine tart... | WE15080050     | 20      | from supplier      |
| Dr. Behr         | Quercetin           | WE-13030084-02 | 40      | not necessary      |
| Dr. Behr         | Red clover extra... | WE12030050-02  | 40      | pending            |

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| Supplier  | Substance           | Batch            | Spectra | Certificate        |
|-----------|---------------------|------------------|---------|--------------------|
| Dr. Behr  | Yam root extract    | WE12040018-01    | 40      | not necessary      |
| Dr. Behr  | Yam root extract    | WE14020005-05    | 40      | pending            |
| El Compra | Chlorella           | WE13010018-01    | 40      | pending            |
| Euro OTC  | Aluminium chlori... | 1109025-01       | 40      | not necessary      |
| Euro OTC  | Aluminium chlori... | 1106017-01       | 40      | not necessary      |
| Euro OTC  | Ammonium chloride   | 1209013-01       | 40      | not necessary      |
| Euro OTC  | Bentonite           | 2903008-01       | 40      | from supplier      |
| Euro OTC  | Calcium carbonat... | 1611008-01       | 20      | not necessary      |
| Euro OTC  | Chromium yeast 0... | L1303028-01      | 40      | 1403474            |
| Euro OTC  | Chromium yeast 0... | L1406030-02      | 60      | not necessary      |
| Euro OTC  | Copper orotate d... | 2106001Z-01      | 40      | not necessary      |
| Euro OTC  | Copper orotate d... | 2106001Z-01      | 40      | not necessary      |
| Euro OTC  | Curcuma extract ... | L1107001         | 40      | not necessary      |
| Euro OTC  | Curcuma extract ... | L1107001         | 40      | pending            |
| Euro OTC  | Curcuma extract ... | L1408013         | 60      | not necessary      |
| Euro OTC  | D-(+)-mannose       | L1503016-01      | 60      | not necessary      |
| Euro OTC  | D-(+)-mannose       | L1111005-02      | 40      | not necessary      |
| Euro OTC  | D-(+)-mannose       | L1111005-02      | 40      | 1405612            |
| Euro OTC  | Devil's claw roo... | 1210003-02       | 40      | 1707472            |
| Euro OTC  | Devil's claw roo... | 1210003-02       | 40      | not necessary      |
| Euro OTC  | Devil's claw roo... | 1210003-02       | 40      | not necessary      |
| Euro OTC  | Dithranole          | 1203025-02       | 40      | not necessary      |
| Euro OTC  | EDTA calcium dis... | 1705029          | 40      | 20170626*          |
| Euro OTC  | Frankincense ext... | 1104005.01       | 40      | AR-12-FG-008694-01 |
| Euro OTC  | Frankincense ext... | 1602008          | 60      | 20160215*          |
| Euro OTC  | Frankincense ext... | 1611023-01       | 60      | 9889               |
| Euro OTC  | Frankincense ext... | 1308020-01       | 60      | 8958               |
| Euro OTC  | Frankincense ext... | 1104005-01       | 40      | pending            |
| Euro OTC  | Frankincense ext... | 1602008          | 60      | 20160215*          |
| Euro OTC  | Heavy magnesium ... | 1205012-01       | 40      | not necessary      |
| Euro OTC  | Heavy magnesium ... | pending          | 27      | AR-12-FG-008488-01 |
| Euro OTC  | Histidine           | 1703022          | 40      | 20170405*          |
| Euro OTC  | L-carnitine tart... | 1708023          | 40      | 20170907*          |
| Euro OTC  | Magnesium carbon... | 2910023          | 40      | from supplier      |
| Euro OTC  | Magnesium oxide,... | 1109031          | 30      | from supplier      |
| Euro OTC  | Magnesium sulfat... | 1202017-01       | 40      | not necessary      |
| Euro OTC  | Magnesium sulfat... | 1109023-01       | 40      | from supplier      |
| Euro OTC  | Magnesium trisil... | 1012032-01       | 40      | AR-13-FG-002912-01 |
| Euro OTC  | Nystatin            | 281103201        | 80      | from supplier      |
| Euro OTC  | Potassium acetate   | 1112007          | 40      | not necessary      |
| Euro OTC  | Potassium hydroc... | 1004019-01       | 70      | from supplier      |
| Euro OTC  | Ropivacaine hydr... | 1707006          | 40      | 20171013*          |
| Euro OTC  | Silicium dioxide    | 1101027-01       | 40      | from supplier      |
| Euro OTC  | Sodium dihydroge... | 1202015-01       | 40      | not necessary      |
| Euro OTC  | Sodium molybdate... | L1305049-01      | 60      | not necessary      |
| Euro OTC  | Sodium molybdate... | L2809007V-02     | 40      | AR-13-FG-002915-01 |
| Euro OTC  | Sodium molybdate... | L1305049-01      | 45      | not necessary      |
| Euro OTC  | Tricalcium phosp... | 1206002-01       | 40      | 1402298            |
| Euro OTC  | Tricalcium phosp... | 1009031-01       | 50      | from supplier      |
| Euro OTC  | Zinc orotate dih... | 1203014-01       | 40      | 1407431            |
| Euro OTC  | Zinc orotate dih... | 1203014-01       | 40      | not necessary      |
| Euro OTC  | Zinc orotate dih... | 13050005-02      | 40      | not necessary      |
| Fagron    | 8-quinolinol sul... | 10F01-N15        | 40      | AR-12-FG-009377-01 |
| Fagron    | 8-quinolinol sul... | 12H21-N08        | 40      | not necessary      |
| Fagron    | Aluminium chlori... | 12I27-N01        | 40      | not necessary      |
| Fagron    | Aluminium potass... | 12F25-N11        | 40      | not necessary      |
| Fagron    | Aluminium potass... | 10B01-N10        | 40      | AR-12-FG-007570-01 |
| Fagron    | Amphetamine sulf... | 15L01-B05-315291 | 20      | 1316Q-03361        |
| Fagron    | Amphetamine sulf... | 13G08-N11        | 20      | 0814K-03361        |
| Fagron    | Amphetamine sulf... | 15L01-B05-315291 | 20      | 1316Q-03361        |

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|----------|---------------------|------------------|---------|--------------------|
| Fagron   | Amphetamine sulf... | 16A29-B03-324577 | 40      | 2017B-03361        |
| Fagron   | Amphetamine sulf... | 16A29-B03-324577 | 40      | 2017B-03361        |
| Fagron   | Barbital sodium     | 12F27-N02        | 20      | 0814I-07775        |
| Fagron   | Barbital sodium     | 15L07-B02-324539 | 40      | 2017A-07775        |
| Fagron   | Barbital sodium     | 15L07-B02-324539 | 40      | 2017A-07775        |
| Fagron   | Barbital sodium     | 14K14-B04-303353 | 20      | 1516I-07775        |
| Fagron   | Barbital sodium     | 14K14-B04-303353 | 20      | 1516I-07775        |
| Fagron   | Betaine hydrochl... | 13H13-N02        | 40      | 1402684            |
| Fagron   | Betaine hydrochl... | 12A03-N08        | 40      | not necessary      |
| Fagron   | Betamethasone-17... | 11I15-N02        | 40      | not necessary      |
| Fagron   | Betamethasone-17... | 11F22-N03        | 40      | AR-13-FG-002911-01 |
| Fagron   | Betamethasone-17... | 11G07IH          | 40      | from supplier      |
| Fagron   | Bromelain           | 14F20-B03295501  | 40      | pending            |
| Fagron   | Bromelain           | 11A10-N10        | 40      | not necessary      |
| Fagron   | Bromelain           | 14F20-B03295501  | 60      | not necessary      |
| Fagron   | Caffeine citrate    | 15A05-B03-302746 | 60      | not necessary      |
| Fagron   | Caffeine citrate    | 11F21-N05        | 40      | not necessary      |
| Fagron   | Caffeine citrate    | 15A05-B03-302746 | 40      | not necessary      |
| Fagron   | Caffeine citrate    | 15A05-B03-318006 | 40      | not necessary      |
| Fagron   | Caffeine citrate    | 12C16-N03        | 40      | 1403477            |
| Fagron   | Caffeine citrate    | 15A05-B03-318006 | 40      | not necessary      |
| Fagron   | Calcium hydroxide   | 10L15-N07        | 30      | not necessary      |
| Fagron   | Calcium hydroxide   | 13E22-N07        | 20      | not necessary      |
| Fagron   | Chlorobutanol he... | 14A06-B31-290310 | 60      | 1412458            |
| Fagron   | Clobetasol-17-pr... | 13E16-N01        | 40      | not necessary      |
| Fagron   | Cocaine hydrochl... | 11G15-N02        | 40      | not necessary      |
| Fagron   | Cocaine hydrochl... | 16B11-B05-323386 | 40      | 1917Q-1278         |
| Fagron   | Cocaine hydrochl... | 16B11-B05-323386 | 40      | 1917Q-1278         |
| Fagron   | Cocaine hydrochl... | 14H27-B03-304551 | 40      | 1917R-01278        |
| Fagron   | Cocaine hydrochl... | 11G28-N11        | 80      | not necessary      |
| Fagron   | Cocaine hydrochl... | 14H27-B03-304551 | 40      | 1917R-01278        |
| Fagron   | Cocaine hydrochl... | 13I17-N02        | 20      | 0814I-01278        |
| Fagron   | Codeine monohydr... | 12C05-N05        | 20      | 0814I-01280        |
| Fagron   | Codeine phosphat... | 13C11-N10        | 20      | 0814I-01279        |
| Fagron   | Codeine phosphat... | 15F09-B02-310520 | 20      | 1316Q-01279        |
| Fagron   | Codeine phosphat... | 15F09-B02-310520 | 20      | 1316Q-01279        |
| Fagron   | Codeine phosphat... | 16E17-B05-324109 | 40      | 2017A-01279        |
| Fagron   | Copper orotate d... | 09F15-N01        | 40      | pending            |
| Fagron   | Copper orotate d... | CH-565313        | 40      | pending            |
| Fagron   | Dexamethasone 1...  | 11G08-N02        | 40      | not necessary      |
| Fagron   | Dexamphetamine s... | 16D20-B01-321049 | 40      | 2017B-03582        |
| Fagron   | Dexamphetamine s... | 13I23-N01        | 20      | 0814M-03582        |
| Fagron   | Dexamphetamine s... | 15H06-B04-313862 | 20      | 1316Q-03582        |
| Fagron   | Dexamphetamine s... | 15H06-B04-313862 | 20      | 1316Q-03582        |
| Fagron   | Dexamphetamine s... | 16F09-B02-328352 | 40      | 2017A-03582        |
| Fagron   | Dexamphetamine s... | 16F09-B02-328352 | 40      | 2017A-03582        |
| Fagron   | Dexamphetamine s... | 11F29N01         | 40      | not necessary      |
| Fagron   | Dihydrocodeine h... | 14K26-B04-306298 | 60      | 1516I-03065        |
| Fagron   | Dihydrocodeine h... | 13H19-N03        | 20      | 0914C-03065        |
| Fagron   | Dihydrocodeine h... | 15F18-B07-323388 | 40      | 2017A-03065        |
| Fagron   | Dihydrocodeine h... | 14K26-B04-306298 | 20      | 1516I-03065        |
| Fagron   | Enalapril maleate   | 16K14-B02-336220 | 40      | 20161227           |
| Fagron   | Ethyl hydrogen f... | 14C12-B07-292760 | 60      | 1410436            |
| Fagron   | Ethyl hydrogen f... | 14C12-B07-292760 | 60      | not necessary      |
| Fagron   | Fentanyl citrate    | 13G30-N06        | 20      | 0814M-07678        |
| Fagron   | Fentanyl citrate    | 11/19-N07        | 40      | from supplier      |
| Fagron   | Fentanyl citrate    | 16E26-B01-525360 | 40      | 2017A-03686        |
| Fagron   | Fentanyl citrate    | 15F18-B01-525098 | 20      | 1316R-03686        |
| Fagron   | Fentanyl citrate    | 15F18-B01-525098 | 20      | 1316R-03686        |
| Fagron   | Fentanyl citrate    | 15F18-B01-525166 | 20      | 1316Q-03686        |

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| Fagron   | Fentanyl citrate    | 4511E-07449      | 80      | from supplier      |
| Fagron   | Fentanyl citrate    | 16E26-B01-525360 | 40      | 2017A-03686        |
| Fagron   | Fentanyl citrate    | 15F18-B01-525166 | 20      | 1316Q-03686        |
| Fagron   | Fuchsine            | 11A05-N08        | 40      | AR-12-FG-002852-01 |
| Fagron   | Glycopyrronium b... | 16E09-B08-331027 | 40      | not necessary      |
| Fagron   | Glycopyrronium b... | 16E09-B08-331027 | 40      | 1707615            |
| Fagron   | Heavy alkaline b... | 11C10-N06        | 40      | AR-13-FG-008124-01 |
| Fagron   | Histidine           | 15I01-B12-329082 | 40      | not necessary      |
| Fagron   | Hydromorphone hy... | 13I25-N05        | 20      | 1516I-01334        |
| Fagron   | Hydromorphone hy... | 13I25-N05        | 20      | 1516I-01334        |
| Fagron   | Hydromorphone hy... | 13E16-N02        | 20      | 0914B-01334        |
| Fagron   | Hydromorphone hy... | 15L08-B08-316877 | 40      | 1917Q-01334        |
| Fagron   | Indigo carmine      | 13K12-N01        | 40      | 1601099            |
| Fagron   | Indigo carmine      | 12C16-N04        | 40      | 1509365            |
| Fagron   | Lithium carbonate   | 08J06-N05        | 30      | not necessary      |
| Fagron   | Macrogol 6000 po... | 14J17-B01-309247 | 60      | not necessary      |
| Fagron   | Macrogol 6000 po... | 12A19-N02        | 40      | AR-13-FG-008919-01 |
| Fagron   | Macrogol 6000 po... | 14J17-B01-309247 | 60      | AR-16-FG-011486-01 |
| Fagron   | Macrogol 6000 po... | 14C11-B01-296014 | 60      | not necessary      |
| Fagron   | Methadone hydroc... | 13J24-B06        | 20      | 0914F-02949        |
| Fagron   | Methadone hydroc... | 16F24-B02-323183 | 40      | 1917Q-02949        |
| Fagron   | Methadone hydroc... | 15E29-B02-313098 | 20      | 1516B-02949        |
| Fagron   | Methadone hydroc... | 15E29-B02-313098 | 20      | 1516B-02949        |
| Fagron   | Methylrosanilini... | 12D19-N01        | 40      | not necessary      |
| Fagron   | Methylrosanilini... | 13H28-N03        | 60      | AR-15-FG-004742-01 |
| Fagron   | Methylrosanilini... | 13H28-N03        | 60      | not necessary      |
| Fagron   | Methylrosanilini... | 12D19-N01        | 40      | 1402202            |
| Fagron   | Methylrosanilini... | 13G03-N11        | 40      | not necessary      |
| Fagron   | Methylrosanilini... | 10A11-N12        | 40      | not necessary      |
| Fagron   | Midazolam           | 13K05-N01        | 20      | 0914E-07393        |
| Fagron   | Midazolam           | 16J03-B09-326963 | 40      | 1917Q-07393        |
| Fagron   | Midazolam           | 14C12-B31-313222 | 20      | 1516A-07393        |
| Fagron   | Midazolam           | 16J03-B09-326963 | 30      | 1917Q-07393        |
| Fagron   | Midazolam           | 14C12-B31-313222 | 20      | 1516A-07393        |
| Fagron   | Midazolam hydroc... | 15J07-B01-320717 | 30      | 1917Q-03538        |
| Fagron   | Midazolam hydroc... | 14L23-B04-300245 | 20      | 1516A-03538        |
| Fagron   | Midazolam hydroc... | 13E22-N09        | 20      | 0914F-03538        |
| Fagron   | Midazolam hydroc... | 14L23-B04-300245 | 20      | 1516A-03538        |
| Fagron   | Midazolam hydroc... | 11F20-N01        | 80      | from supplier      |
| Fagron   | Midazolam hydroc... | 15J07-B01-320717 | 40      | 1917Q-03538        |
| Fagron   | Midazolam hydroc... | 15H04-B03-314396 | 30      | 1917R-03538        |
| Fagron   | Morphine hydroch... | 15I09-B08-312694 | 20      | 1416Q-01879        |
| Fagron   | Morphine hydroch... | 15I09-B08-312694 | 20      | 1416Q-01879        |
| Fagron   | Morphine hydroch... | 16D21-B02-322088 | 40      | 1917Q-01879        |
| Fagron   | Morphine hydroch... | 16D21-B02-322088 | 40      | 1917Q-01879        |
| Fagron   | Morphine hydroch... | 13G08-N04        | 20      | 0914G-01879        |
| Fagron   | Morphine sulfate    | 13J07-N04        | 20      | 0914G-07776        |
| Fagron   | Morphine sulfate    | 14F02-B06-315405 | 40      | 1917Q-07776        |
| Fagron   | Morphine sulfate    | 14F02-B06-315405 | 40      | 1917Q-07776        |
| Fagron   | Noscapine hydroc... | 12D04-B04-284297 | 40      | not necessary      |
| Fagron   | Phenobarbital       | 15G07-B06-311718 | 20      | 1416Q-01040        |
| Fagron   | Phenobarbital       | 16G20-B04-328344 | 40      | 2017B-01040        |
| Fagron   | Phenobarbital       | 15G07-B06-311718 | 20      | 1416Q-01040        |
| Fagron   | Phenobarbital       | 16G20-B04-328344 | 40      | 2017B-01040        |
| Fagron   | Prednisolone 1:1... | 09107-N09        | 40      | not necessary      |
| Fagron   | Prednisolone 1:1... | 11L13-N06        | 40      | AR-13-FG-000835-01 |
| Fagron   | Rutoside trihydr... | 13K12-B06-295483 | 60      | not necessary      |
| Fagron   | Rutoside trihydr... | 11I20-N02        | 40      | AR-13-FG-000836-01 |
| Fagron   | Silver protein      | 10F01-N13        | 50      | not necessary      |
| Fagron   | Silver protein a... | 18000970         | 40      | not necessary      |

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|------------------|-------------------------|--------------------|---------|--------------------|
| Fagron           | Sodium alginate         | 14G22-B99-297091   | 60      | not necessary      |
| Fagron           | Sodium alginate         | 11K17-N12          | 40      | AR-13-FG-002913-01 |
| Fagron           | Sodium hydroxide...     | 12E02-N15          | 80      | not necessary      |
| Fagron           | Sodium monohydro...     | 11E02-N14          | 40      | not necessary      |
| Fagron           | Sodium monohydro...     | 09K02-N05          | 40      | not necessary      |
| Fagron           | Sodium thiosulfa...     | 11612-N16          | 40      | AR-13-FG-005752-01 |
| Fagron           | Thiamine nitrate        | 15A30-B06-309069   | 60      | AR-16-FG-005855-01 |
| Fagron           | Thiomersal              | 11K01-N03          | 40      | 1401417            |
| Fagron           | Triamcinolone ac...     | 08K26-N05          | 40      | from supplier      |
| Fagron           | Zinc orotate dihydro... | 11K16-N10          | 40      | not necessary      |
| Fagron           | Zinc orotate dihydro... | 13J08-N05          | 40      | not necessary      |
| Galke            | Abrotani herb, cut      | 21340              | 40      | not necessary      |
| Galke            | Acorus root, peeled...  | 19657              | 40      | not necessary      |
| Galke            | Blackberry leaf,...     | 18060              | 40      | not necessary      |
| Galke            | Boldo leaf, cut         | 19855              | 40      | not necessary      |
| Galke            | Fraxinella root,...     | 17805              | 40      | not necessary      |
| Galke            | Hawthorn leaf with...   | 21126              | 40      | not necessary      |
| Galke            | Juniper                 | 19174              | 40      | not necessary      |
| Galke            | Liquorice root, ...     | 22728              | 40      | from supplier      |
| Galke            | Marshmallow root...     | 14073              | 40      | not necessary      |
| Galke            | Maté leaf, cut          | 21684              | 40      | from supplier      |
| Galke            | Matricaria flower       | 22684              | 40      | not necessary      |
| Galke            | Melissa leaf, cut       | 22218              | 40      | from supplier      |
| Galke            | Nettle leaf, cut        | 21238              | 40      | from supplier      |
| Galke            | Nettle seed             | 21186              | 40      | pending            |
| Galke            | Peppermint leaf,...     | 20244              | 40      | not necessary      |
| Galke            | Peppermint leaf,...     | 19537              | 40      | not necessary      |
| Galke            | Silverweed, cut         | 22840              | 40      | not necessary      |
| Galke            | Thyme, rubbed           | 21932              | 40      | not necessary      |
| Gatt-Koller      | Caffeine citrate        | 4065/11164916      | 40      | not necessary      |
| Gatt-Koller      | Caffeine citrate        | 1783/05140715      | 60      | AR-15-FG-014994-01 |
| GoCaps           | Gelatine capsules       | 650-004            | 37      | AR-12-FG-010178-01 |
| Gonmisol         | Lutein 20% powder       | 20120320           | 40      | not necessary      |
| Gustav-G. Die... | Chondroitin sulf...     | pending            | 40      | AR-14-FG-001918-01 |
| Hepart           | Glucosamine sulf...     | 0909015            | 40      | not necessary      |
| Hepart           | Inositol hexanic...     | 022901             | 40      | not necessary      |
| inalc            | D-ribose                | P19/28/069         | 20      | not necessary      |
| Inresa           | Baclofen                | 206031617/09062017 | 40      | AR-17-FG-018577-01 |
| Inresa           | Ketoprofen              | F1300183           | 60      | AR-15-FG-009572-01 |
| Inresa           | Ketoprofen              | F1300182           | 60      | not necessary      |
| Inresa           | Maltodextrin            | R1503902           | 60      | AR-15-FG-008821-01 |
| Inresa           | Maltodextrin            | R1600014           | 60      | not necessary      |
| Inresa           | Sotalol hydrochl...     | 369-MC             | 40      | not necessary      |
| iphas            | Cellulose capsules      | 53099151           | 37      | not necessary      |
| Kaden Biochem... | Antioxidant tea ...     | 0809               | 40      | not necessary      |
| Kaden Biochem... | Quercetin               | 0608               | 40      | not necessary      |
| Kaden Biochem... | Rhodiola rosea e...     | 1009               | 40      | pending            |
| Kaden Biochem... | Rhodiola rosea e...     | 1009               | 40      | not necessary      |
| Klenk            | Abrotani herb, cut      | 3451B110207        | 40      | not necessary      |
| Klenk            | Agarikon                | 1061A120312        | 40      | pending            |
| Klenk            | Agnus castus fruit      | 7110N090701        | 40      | pending            |
| Klenk            | Almonds, bitter,...     | 0040A111117        | 40      | not necessary      |
| Klenk            | Ammi visnaga fruit      | 7120A120112        | 40      | not necessary      |
| Klenk            | Angelica root           | 6085B120614        | 60      | 1509356            |
| Klenk            | Angelica root           | 6085B120614        | 40      | not necessary      |
| Klenk            | Aniseed                 | 2700A140129        | 60      | not necessary      |
| Klenk            | Aniseed                 | 2700A110701        | 40      | not necessary      |
| Klenk            | Aniseed                 | 2700A160511        | 60      | 1708049            |
| Klenk            | Ash bark, cut           | 0871B110127        | 60      | not necessary      |
| Klenk            | Asparagus root, ...     | 6151B110304        | 40      | 1403480            |

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| Klenk    | Asplenium scolop... | 4451B100520 | 40      | not necessary      |
| Klenk    | Barberries          | 2720N111109 | 40      | 1405127            |
| Klenk    | Barberry root ba... | 0551B100706 | 40      | not necessary      |
| Klenk    | Basil, rubbed       | 3632A110201 | 40      | not necessary      |
| Klenk    | Bean shells, cut    | 067A100817  | 40      | from supplier      |
| Klenk    | Birch bark, cut     | 0561A121121 | 40      | not necessary      |
| Klenk    | Bitter fennel       | 2880N120418 | 40      | 1412547            |
| Klenk    | Bitter fennel       | pending     | 40      | AR-12-FG-007350-01 |
| Klenk    | Bitter fennel       | 2860A140613 | 60      | AR-15-FG-008160-01 |
| Klenk    | Bitter fennel       | 2880N120418 | 40      | AR-15-FG-002805-02 |
| Klenk    | Bitter orange pe... | pending     | 40      | not necessary      |
| Klenk    | Black cumin seed    | 7330A110204 | 40      | not necessary      |
| Klenk    | Black mustard seed  | 7430A120813 | 40      | AR-15-FG-001050-01 |
| Klenk    | Black mustard se... | 7434A120712 | 40      | AR-15-FG-006711-01 |
| Klenk    | Blackthorn flowe... | 1150N101109 | 40      | not necessary      |
| Klenk    | Blessed thistle,... | 3691A110517 | 40      | not necessary      |
| Klenk    | Bogbean leaf, cut   | 2371B100616 | 40      | AR-12-FG-007208-01 |
| Klenk    | Boldo leaf, cut     | 1911A100714 | 40      | not necessary      |
| Klenk    | Buckwheat seed      | 7510A111011 | 60      | pending            |
| Klenk    | Buckwheat seed      | 7510A111011 | 40      | from supplier      |
| Klenk    | Calendula flower    | 1241B130321 | 40      | not necessary      |
| Klenk    | Calendula flower... | 1241B110118 | 40      | from supplier      |
| Klenk    | Calendula flower... | 1241A100816 | 40      | not necessary      |
| Klenk    | Caraway fruit       | 2770A100413 | 40      | not necessary      |
| Klenk    | Caraway fruit       | 2770A110601 | 40      | pending            |
| Klenk    | Caraway fruit       | 2770A110601 | 40      | pending            |
| Klenk    | Caraway fruit       | 2770A110601 | 40      | pending            |
| Klenk    | Cardamom, excort... | 2765A130524 | 60      | AR-15-FG-015285-01 |
| Klenk    | Celery fruit        | 7140A111013 | 40      | not necessary      |
| Klenk    | Celery fruit        | 7140A130625 | 40      | 1405177            |
| Klenk    | Celery fruit        | 7140A131122 | 60      | not necessary      |
| Klenk    | Celery root, cut    | 6091N081016 | 40      | pending            |
| Klenk    | Celery root, cut    | 6091A110110 | 40      | 1410177            |
| Klenk    | Ceylon cinnamon,... | 0614B120504 | 40      | not necessary      |
| Klenk    | Ceylon cinnamon,... | 0614B120504 | 40      | 1403047            |
| Klenk    | Chelidonium maju... | 3731K120904 | 40      | not necessary      |
| Klenk    | Cherry stems, cut   | 5591A100913 | 40      | 1402575            |
| Klenk    | Chervil, rubbed     | 3721A100329 | 40      | not necessary      |
| Klenk    | Chicory herb, cut   | 3751A100118 | 40      | not necessary      |
| Klenk    | Chicory root, cut   | 6221A101202 | 40      | from supplier      |
| Klenk    | Cleavers goosegr... | 4731B110809 | 40      | not necessary      |
| Klenk    | Clove               | 1260A110608 | 40      | not necessary      |
| Klenk    | Clove               | 1260A150916 | 40      | 1708050            |
| Klenk    | Clove, powdered ... | 1264B141007 | 60      | AR-15-FG-014858-01 |
| Klenk    | Cocoa bark, cut     | 0571N101012 | 40      | not necessary      |
| Klenk    | Coltsfoot leaf, ... | 2021B111005 | 40      | not necessary      |
| Klenk    | Comfrey herb, cut   | 4561B100518 | 60      | not necessary      |
| Klenk    | Comfrey root        | 6241A090616 | 70      | F 2010 000 067     |
| Klenk    | Comfrey root        | 6244B130624 | 40      | not necessary      |
| Klenk    | Cottonwood bud, ... | 3266B130826 | 40      | 1410178            |
| Klenk    | Cottonwood bud, ... | 3266B101208 | 40      | not necessary      |
| Klenk    | Cottonwood bud, ... | 3266B150624 | 60      | not necessary      |
| Klenk    | Cumin, powdered     | 2824B121001 | 40      | not necessary      |
| Klenk    | Dandelion root, ... | 6621B151029 | 60      | AR-17-FG-007535-01 |
| Klenk    | Dandelion root, ... | 6621A100510 | 40      | not necessary      |
| Klenk    | Devil's claw root   | 6334B110706 | 40      | from supplier      |
| Klenk    | Dill fruit          | 2680A170222 | 60      | not necessary      |
| Klenk    | Dill fruit          | 2680A110808 | 40      | not necessary      |
| Klenk    | Dill fruit          | pending     | 40      | not necessary      |
| Klenk    | Elder berries       | 3010A120202 | 40      | pending            |

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| Supplier | Substance            | Batch       | Spectra | Certificate        |
|----------|----------------------|-------------|---------|--------------------|
| Klenk    | Elder leaf, cut      | 2321B130221 | 60      | not necessary      |
| Klenk    | Elder root, cut      | 6281B110427 | 40      | not necessary      |
| Klenk    | Elecampane rhizo...  | 6341B120611 | 40      | not necessary      |
| Klenk    | Euphrasy herb, cut   | 3871B100713 | 40      | not necessary      |
| Klenk    | European golden ...  | 1781B110706 | 40      | not necessary      |
| Klenk    | Fenugreek, powde...  | 7264A151001 | 60      | AR-16-FG-014493-01 |
| Klenk    | Fenugreek, powde...  | 7264B130205 | 40      | 1408080            |
| Klenk    | Frangula bark, cut   | 0661B110412 | 40      | not necessary      |
| Klenk    | Galeopsis herb, ...  | 3911A090219 | 40      | not necessary      |
| Klenk    | Ginger, peeled       | 6951B100302 | 60      | not necessary      |
| Klenk    | Ginger, peeled, ...  | 6954B150325 | 60      | 1606616            |
| Klenk    | Ginger, peeled, ...  | 6554B100409 | 40      | AR-12-FG-008593-01 |
| Klenk    | Ginger, peeled, ...  | 6954B160429 | 60      | 1704440            |
| Klenk    | Ginger, peeled, ...  | 6954B170127 | 60      | 1708675            |
| Klenk    | Ginger, peeled, ...  | 6954B140724 | 60      | AR-15-FG-014915-01 |
| Klenk    | Goat's rue, cut      | 3901C110905 | 40      | not necessary      |
| Klenk    | Greek mountain h...  | 4511K130314 | 40      | not necessary      |
| Klenk    | Green tea            | 5100A100611 | 40      | not necessary      |
| Klenk    | Ground ivy herb,...  | 3991B110304 | 40      | not necessary      |
| Klenk    | Hawthorn flower      | pending     | 40      | not necessary      |
| Klenk    | Hawthorn leaf wi...  | 1971A110125 | 45      | not necessary      |
| Klenk    | Hawthorn leaf wi...  | 1971A100830 | 40      | not necessary      |
| Klenk    | Hay flower           | 1400A130304 | 40      | not necessary      |
| Klenk    | Hay flower           | 1400A120116 | 40      | not necessary      |
| Klenk    | Horse chestnut f...  | 1441B100616 | 40      | not necessary      |
| Klenk    | Ispaghula seed       | 7560A120330 | 40      | 1403467            |
| Klenk    | Java tea, cut        | 2221B101213 | 40      | not necessary      |
| Klenk    | Java tea, cut        | 2221B110718 | 40      | not necessary      |
| Klenk    | Juniper              | 2890A100120 | 40      | not necessary      |
| Klenk    | Juniper, powdered    | 2894B150922 | 60      | 1704439            |
| Klenk    | Juniper, powdered    | 2894B130320 | 40      | 1411362            |
| Klenk    | Juniper, powdered    | 2894B100531 | 40      | pending            |
| Klenk    | Knotgrass, cut       | 4301A120912 | 40      | not necessary      |
| Klenk    | Ladys bedstraw ...   | 3921B091126 | 40      | not necessary      |
| Klenk    | Ladys bedstraw ...   | 3921B101012 | 40      | not necessary      |
| Klenk    | Ladys bedstraw ...   | 3921B101012 | 40      | not necessary      |
| Klenk    | Laurel leaf, cut     | 2121B101209 | 40      | not necessary      |
| Klenk    | Laurel leaf, cut     | 2121B110809 | 40      | not necessary      |
| Klenk    | Laurel leaf, pow...  | 2124A110329 | 60      | not necessary      |
| Klenk    | Laurel leaf, pow...  | 2124A110329 | 40      | not necessary      |
| Klenk    | Laurel leaf, pow...  | 2124A110329 | 40      | 1411032            |
| Klenk    | Laurel seed          | 2900N100517 | 75      | not necessary      |
| Klenk    | Lavender flower      | 1489A120103 | 40      | from supplier      |
| Klenk    | Lavender flower      | 1489A120103 | 40      | not necessary      |
| Klenk    | Lavender flower      | 06120       | 40      | from supplier      |
| Klenk    | Lime leaf, cut       | 2471B110126 | 40      | not necessary      |
| Klenk    | Linseed              | 7308A100705 | 40      | not necessary      |
| Klenk    | Lovage root, cut     | 6371A080508 | 40      | AR-12-FG-008337-01 |
| Klenk    | Mace, powdered (...) | 5214A090716 | 50      | pending            |
| Klenk    | Maize style, cut     | 5581A111206 | 40      | not necessary      |
| Klenk    | Male speedwell w...  | 4661B101011 | 40      | not necessary      |
| Klenk    | Male speedwell w...  | 4661B101011 | 40      | not necessary      |
| Klenk    | Mallow leaf, cut     | 2131B101014 | 50      | not necessary      |
| Klenk    | Mallow leaf, cut     | 2131B110420 | 40      | not necessary      |
| Klenk    | Marian thistle h...  | 3701B110610 | 40      | not necessary      |
| Klenk    | Marian thistle h...  | 3701A100916 | 40      | not necessary      |
| Klenk    | Marian thistle h...  | 3701A111207 | 40      | not necessary      |
| Klenk    | Marshmallow root...  | 6074B100416 | 40      | not necessary      |
| Klenk    | Marshmallow root...  | pending     | 40      | not necessary      |
| Klenk    | Marshmallow root...  | 6071A100210 | 40      | not necessary      |

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| Supplier | Substance           | Batch       | Spectra | Certificate        |
|----------|---------------------|-------------|---------|--------------------|
| Klenk    | Meadowsweet herb... | 4541A120313 | 60      | not necessary      |
| Klenk    | Melissa leaf, cut   | 2161A090630 | 130     | not necessary      |
| Klenk    | Melissa leaf, cut   | 2161A121029 | 55      | not necessary      |
| Klenk    | Melissa leaf, cut   | 2161A101216 | 40      | not necessary      |
| Klenk    | Motherwort herb,... | 4071A121211 | 40      | not necessary      |
| Klenk    | Myrrh               | 3355B120628 | 40      | AR-15-FG-000945-01 |
| Klenk    | Nettle leaf, cut    | 2381A110913 | 40      | not necessary      |
| Klenk    | Nettle root, cut    | 6631B100211 | 40      | from supplier      |
| Klenk    | Nettle root, cut    | 6631B120416 | 40      | not necessary      |
| Klenk    | Nettle seed         | 7470A111117 | 35      | pending            |
| Klenk    | Nettle seed         | 7470A110418 | 40      | not necessary      |
| Klenk    | Nutmeg              | 7320A121002 | 40      | not necessary      |
| Klenk    | Nutmeg, powdered... | 7325A160405 | 60      | 9888               |
| Klenk    | Olive leaf          | 211A080311  | 40      | AR-12-FG-008663-01 |
| Klenk    | Orange peel, cut    | 0531A091125 | 40      | not necessary      |
| Klenk    | Oregano herb        | 4221A100628 | 40      | not necessary      |
| Klenk    | Oregano herb        | 4221N111011 | 40      | not necessary      |
| Klenk    | Parsley herb, ru... | 4262A091116 | 60      | not necessary      |
| Klenk    | Parsley root, cut   | 6441A110210 | 40      | not necessary      |
| Klenk    | Parsley seed        | 7370A130909 | 40      | 1407600            |
| Klenk    | Parsley seed        | 7370A091120 | 40      | not necessary      |
| Klenk    | Passionflower he... | 4231A120329 | 40      | not necessary      |
| Klenk    | Passionflower he... | 4231B080508 | 30      | from supplier      |
| Klenk    | Passionflower he... | 4231A100705 | 49      | from supplier      |
| Klenk    | Peony root, cut     | 6421B120327 | 60      | not necessary      |
| Klenk    | Peony root, cut     | 6421B090625 | 40      | from supplier      |
| Klenk    | Peppermint leaf,... | 2181A100323 | 40      | not necessary      |
| Klenk    | Peppermint leaf,... | 2181A101013 | 40      | not necessary      |
| Klenk    | Peppermint leaf,... | pending     | 20      | not necessary      |
| Klenk    | Peppermint leaf,... | 2181A110512 | 40      | not necessary      |
| Klenk    | Primrose root, cut  | 6461A100511 | 40      | not necessary      |
| Klenk    | Primrose root, cut  | 6461N100203 | 40      | from supplier      |
| Klenk    | Red clover flower   | 1640A100120 | 40      | not necessary      |
| Klenk    | Red clover flower   | 1640A100120 | 40      | not necessary      |
| Klenk    | Red poppy petals... | 1531B090126 | 40      | not necessary      |
| Klenk    | Restharrow root,... | 6411B130404 | 40      | not necessary      |
| Klenk    | Ribwort plantain... | 4271A100615 | 40      | not necessary      |
| Klenk    | Rose hips seed      | 7240A120402 | 60      | not necessary      |
| Klenk    | Rose hips with p... | 2841B111019 | 40      | not necessary      |
| Klenk    | Rosemary leaf, cut  | 2261A131118 | 60      | AR-15-FG-008499-01 |
| Klenk    | Ruscus rhizome, ... | 7081B110301 | 60      | not necessary      |
| Klenk    | Saffron (spice)     | 0384A121022 | 40      | not necessary      |
| Klenk    | Sage leaf, cut      | 2301A110420 | 40      | not necessary      |
| Klenk    | Sage leaf, cut      | 2301A100208 | 40      | not necessary      |
| Klenk    | Sage leaf, cut      | 2301A100209 | 30      | not necessary      |
| Klenk    | Sage leaf, cut      | 2301A100209 | 40      | not necessary      |
| Klenk    | Sanicle herb, cut   | 4391B110411 | 50      | from supplier      |
| Klenk    | Saponaria herb, ... | 4411A090915 | 40      | not necessary      |
| Klenk    | Senna leaf, powd... | 2334B130606 | 60      | AR-15-FG-015212-01 |
| Klenk    | Senna leaf, powd... | 2334B090306 | 50      | pending            |
| Klenk    | Senna leaf, powd... | 2334B110207 | 40      | pending            |
| Klenk    | St. John's wort,... | 4021A100315 | 20      | not necessary      |
| Klenk    | St. John's wort,... | 4021A100819 | 50      | not necessary      |
| Klenk    | Stemless carline... | 6194B091028 | 50      | from supplier      |
| Klenk    | Strawberry leaf,... | 2031B110224 | 40      | not necessary      |
| Klenk    | Strawberry leaf,... | 2031B120925 | 40      | not necessary      |
| Klenk    | Strawberry leaf,... | 2031B110224 | 40      | not necessary      |
| Klenk    | Sunflower, cut      | 1701B100902 | 40      | not necessary      |
| Klenk    | Sweet fennel        | 2870A110412 | 40      | pending            |
| Klenk    | Sweet fennel        | 2870A130304 | 40      | 1405154            |

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| Supplier        | Substance           | Batch            | Spectra | Certificate        |
|-----------------|---------------------|------------------|---------|--------------------|
| Klenk           | Tall hawkweed, cut  | 3611B111005      | 40      | not necessary      |
| Klenk           | Theriac, powdered   | 13816            | 60      | 1705088            |
| Klenk           | Thyme, rubbed       | 4622A110728      | 40      | not necessary      |
| Klenk           | Tonka beans         | 1030A110704      | 40      | not necessary      |
| Klenk           | Tormentil           | 6914B120112      | 40      | not necessary      |
| Klenk           | Tormentil           | 6911B141114      | 60      | AR-15-FG-014020-01 |
| Klenk           | Turmeric root, cut  | 6741A110202      | 40      | AR-12-FG-008355-01 |
| Klenk           | Verbena herb, cut   | 4651B120611      | 40      | not necessary      |
| Klenk           | Vine leaf, cut      | 2491B100707      | 40      | not necessary      |
| Klenk           | White mustard se... | 7254A110823      | 40      | 1403282            |
| Klenk           | White mustard se... | 7254A110823      | 40      | not necessary      |
| Klenk           | Wild pansy, cut     | 4681A100621      | 40      | not necessary      |
| Klenk           | Wild pansy, cut     | 4681B100624      | 40      | not necessary      |
| Klenk           | Wild pansy, cut     | 4681B100624      | 40      | not necessary      |
| Klenk           | Willow bark, cut    | 0811B100910      | 40      | not necessary      |
| Klenk           | Willowherb, smal... | 4721A140203      | 60      | not necessary      |
| Klenk           | Willowherb, smal... | 4721A101010      | 40      | not necessary      |
| Klenk           | Willowherb, smal... | 4721A101010      | 40      | not necessary      |
| Klenk           | Yarrow herb, cut    | 4181A111122      | 40      | not necessary      |
| Klenk           | Yarrow herb, cut    | 4181A111122      | 40      | not necessary      |
| Klenk           | Yarrow herb, cut    | 4181A111122      | 40      | not necessary      |
| Klenk           | Yarrow herb, cut    | 4181A091111      | 60      | not necessary      |
| Klenk           | Zedoary root, po... | 6944B080904      | 50      | pending            |
| Kräuter Schulte | Albizia julibris... | 42681            | 40      | from supplier      |
| Kräuter Schulte | Anemarrhena root... | 37601            | 30      | from supplier      |
| Kräuter Schulte | Angelica root       | 46957            | 40      | pending            |
| Kräuter Schulte | Angelica root       | 53855            | 40      | pending            |
| Kräuter Schulte | Angelica root       | 48123            | 40      | not necessary      |
| Kräuter Schulte | Aniseed             | 51600            | 40      | not necessary      |
| Kräuter Schulte | Black cumin seed    | 50371            | 40      | not necessary      |
| Kräuter Schulte | Caraway fruit       | 53193            | 40      | pending            |
| Kräuter Schulte | China Pai Mu Tan    | 54071            | 40      | from supplier      |
| Kräuter Schulte | Dryas octopetala... | 38970            | 39      | from supplier      |
| Kräuter Schulte | Feverfew herb, cut  | 54169            | 40      | from supplier      |
| Kräuter Schulte | Geum urbanum her... | 52944            | 40      | from supplier      |
| Kräuter Schulte | Grassleaf sweetf... | 32477            | 40      | from supplier      |
| Kräuter Schulte | Hawthorn leaf wi... | 52923            | 40      | from supplier      |
| Kräuter Schulte | Liquorice root, ... | 48219            | 40      | not necessary      |
| Kräuter Schulte | Long-stamen chive   | 10445            | 40      | pending            |
| Kräuter Schulte | Long-stamen chive   | 50126            | 40      | pending            |
| Kräuter Schulte | Marian thistle f... | 53673            | 40      | from supplier      |
| Kräuter Schulte | Marshmallow root... | 46559            | 40      | from supplier      |
| Kräuter Schulte | Moroccan mint, cut  | 44201            | 40      | pending            |
| Kräuter Schulte | Red tea             | 52029            | 40      | pending            |
| Kräuter Schulte | Ribwort plantain... | 47935            | 40      | from supplier      |
| Kräuter Schulte | Saponaria root, ... | 53638            | 40      | from supplier      |
| Kräuter Schulte | Thyme, rubbed       | 47177            | 40      | not necessary      |
| Kräuter Schulte | Twotoothed achyr... | 45053            | 40      | not necessary      |
| Kräuter Schulte | Twotoothed achyr... | 42168            | 40      | pending            |
| Kräuter Schulte | Water plantain r... | 52179            | 40      | from supplier      |
| Kräuter Schulte | White mustard seed  | 52071            | 40      | 1408078            |
| Kräuter Schulte | Wild apple, sweet   | 53182            | 40      | not necessary      |
| Kräuter Schulte | Zedoary root, cut   | 53227            | 40      | not necessary      |
| kreatin GmbH    | Creatine            | 300331           | 50      | not available      |
| Lycored corp.   | Caromix             | CMX-PL-101112    | 40      | not necessary      |
| Lycored corp.   | Caromix             | CMX-LLCV-011401  | 40      | not necessary      |
| Merck KGaA      | Benzoyl peroxide... | S7012241509      | 60      | pending            |
| Merck KGaA      | Caesium carbonate   | K36017440634     | 40      | from supplier      |
| mikroChem       | D-(+)-mannose       | A-04052011/R3878 | 40      | not necessary      |
| MP Biomedicals  | Sulfanilamide       | M3567            | 40      | 1402054            |

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| Supplier         | Substance               | Batch      | Spectra | Certificate        |
|------------------|-------------------------|------------|---------|--------------------|
| Otto Fischar     | Talcum                  | 90841/1    | 40      | from supplier      |
| Pharmorgana      | L-carnitine tart...     | 1000160672 | 40      | not necessary      |
| Pharmorgana      | Sodium dichloroa...     | 1000150016 | 40      | from supplier      |
| Pharmorgana      | Zinc orotate dihydro... | 1000127154 | 40      | not necessary      |
| Phytochem        | D-ribose                | pending    | 60      | not necessary      |
| Phytochem        | D-ribose                | pending    | 40      | not necessary      |
| Roth             | Brilliant blue R...     | 314217301  | 60      | from supplier      |
| Roth             | Deoxycholic acid...     | 084181622  | 40      | 1405618            |
| Roth             | Deoxycholic acid...     | 385212633  | 60      | not necessary      |
| Roth             | Deoxycholic acid...     | 154212633  | 60      | not necessary      |
| Roth             | Deoxycholic acid...     | 351172090  | 40      | not necessary      |
| Roth             | Esculin                 | 155206581  | 60      | pending            |
| Roth             | Theobromine, 99%        | 145191010  | 60      | AR-16-FG-002141-01 |
| Roth             | Theobromine, 99%        | 365191010  | 60      | not necessary      |
| Roth             | Trypan blue (C.I...     | 204209355  | 60      | from supplier      |
| Safic-Alcan      | Amygdalin               | 11082101   | 40      | from supplier      |
| Safic-Alcan      | Amygdalin, bitte...     | BAE150902  | 20      | from supplier      |
| Safic-Alcan      | Amygdalin, bitte...     | BAE150902  | 20      | from supplier      |
| Safic-Alcan      | Cowberry extract...     | 17320/01   | 40      | AR-12-FG-008822-01 |
| Sanacorp         | Yarrow herb, cut        | 11280503   | 40      | from supplier      |
| Sand 12 GmbH     | D-ribose                | L201211720 | 40      | not necessary      |
| sanherb          | Griffonia seed e...     | G-S100915  | 40      | from supplier      |
| Sigma-Aldrich    | Bromelain               | BCBM1589V  | 40      | not necessary      |
| Sigma-Aldrich    | Bromothymol blue        | MKBQ5404V  | 40      | pending            |
| softline         | Maltodextrin            | 940PLV-643 | 40      | not necessary      |
| Spinnrad         | Emulsan II SP           | 111300063  | 40      | from supplier      |
| Spinnrad         | Inulin                  | 2013481819 | 30      | not necessary      |
| Spinnrad         | Inulin                  | 1112300433 | 40      | not necessary      |
| Th. Geyer        | Amphetamine sulf...     | 67002      | 20      | 0814I-03361        |
| Th. Geyer        | Amphetamine sulf...     | 67002      | 40      | not necessary      |
| Th. Geyer        | Amphetamine sulf...     | 067043     | 40      | 2017C-03361        |
| Th. Geyer        | Amphetamine sulf...     | 067043     | 40      | 2017C-03361        |
| Th. Geyer        | Barbital sodium         | 60508      | 40      | not available      |
| Th. Geyer        | Barbital sodium         | 60508      | 80      | not necessary      |
| Th. Geyer        | Calcium colamine...     | 260EXP1016 | 40      | from supplier      |
| Th. Geyer        | Calcium colamine...     | 260EXP1016 | 40      | from supplier      |
| Th. Geyer        | Calcium colamine...     | 33299      | 20      | from supplier      |
| Th. Geyer        | Cocaine hydrochl...     | 60145      | 20      | 0814K-01278        |
| Th. Geyer        | Codeine phosphat...     | 067054     | 40      | 2017D-01279        |
| Th. Geyer        | Codeine phosphat...     | 067054     | 40      | 2017D-01279        |
| Th. Geyer        | Codeine phosphat...     | 67038      | 20      | 0814K-01279        |
| Th. Geyer        | Dihydrocodeine h...     | 67035      | 20      | 0914D-03065        |
| Th. Geyer        | Dihydrocodeine h...     | 067052     | 40      | 2017D-03065        |
| Th. Geyer        | Methadone hydroc...     | 067055     | 40      | 1917S-02949        |
| Th. Geyer        | Methadone hydroc...     | 67033      | 20      | 0914G-02949        |
| Th. Geyer        | Methadone hydroc...     | 067055     | 40      | 1917S-02949        |
| Th. Geyer        | Methadone hydroc...     | 67047      | 20      | 0914H-02949        |
| Th. Geyer        | Mg-Ca-K colamine...     | 36985      | 20      | from supplier      |
| Th. Geyer        | Mg-Ca-K colamine...     | 117EXP1016 | 40      | from supplier      |
| Th. Geyer        | Mg-Ca-K colamine...     | 54610      | 40      | from supplier      |
| Th. Geyer        | Mg-Ca-K colamine...     | 117EXP1016 | 40      | from supplier      |
| Th. Geyer        | Mg-Ca-K colamine...     | 54610      | 40      | not necessary      |
| Th. Geyer        | Morphine hydroch...     | 67036      | 20      | 0914H-01879        |
| Th. Geyer        | Morphine hydroch...     | 56311      | 40      | not necessary      |
| Th. Geyer        | Phenobarbital           | 067056     | 40      | 2017A-01040        |
| Th. Geyer        | Phenobarbital           | 67045      | 20      | 0914F-01040        |
| Vitatene         | Betanat® 10% CWD        | 400101E10  | 40      | not necessary      |
| Vitaworld        | D-(+)-mannose           | 5449324    | 40      | not necessary      |
| VMP Chemiekon... | D-(+)-glucosamin...     | 144212943  | 40      | 20140402           |
| Wellmune         | 1.25-beta-glucan        | 10176-021  | 40      | not necessary      |

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| <b>Supplier</b> | <b>Substance</b>    | <b>Batch</b> | <b>Spectra</b> | <b>Certificate</b> |
|-----------------|---------------------|--------------|----------------|--------------------|
| pending         | Bromothymol blue    | pending      | 40             | not necessary      |
| pending         | Chicory root, cut   | pending      | 20             | not necessary      |
| pending         | Common broom her... | pending      | 40             | not necessary      |
| pending         | Dandelion herb w... | pending      | 40             | not necessary      |
| pending         | Kaolin, heavy       | pending      | 50             | not necessary      |
| pending         | Magnesium sulfat... | pending      | 40             | not necessary      |
| pending         | Male speedwell w... | pending      | 40             | not necessary      |
| pending         | Melissa leaf, cut   | pending      | 45             | not necessary      |
| pending         | Naloxone hydroch... | pending      | 40             | not necessary      |
| pending         | Potassium monohy... | pending      | 40             | not necessary      |
| pending         | Sage leaf, cut      | pending      | 40             | not necessary      |
| pending         | Sodium butyrate     | pending      | 40             | not necessary      |
| pending         | Sodium proprionate  | pending      | 40             | not necessary      |
| pending         | Sodium thiosulfa... | pending      | 40             | AR-13-FG-001882-01 |
| pending         | Tragacanth, powd... | pending      | 40             | not necessary      |

\*The spectra were taken from a part of the same sample which the supplier used for its analysis (identity, purity, content). In this case the manufacturer certificates proof the identity and quality of the sample from those the spectra descend.



## Appendix C: Additional validation samples (Type C)

Spectra for substances from the field which cannot be identified with this model also enter the validation. In this manner, it is verified that the model also rejects unknown substances. The spectra for these samples were recorded by *Apo-Ident* customers. They belong to *Type C*. The information provided by the customer regarding the manufacturer and batch number is taken over by *HiperScan GmbH* to a large extent unchecked.

The samples originate from 8545 batches. From these, 20 975 spectra were recorded. The spectra recorded on independent samples of substances from the field which can be identified with the model are listed respectively in the section *Type C* for the individual substances and do not appear again elsewhere in this list.

| Supplier                  | Substance                | Batch          | Spectra |
|---------------------------|--------------------------|----------------|---------|
| A.H. 27.05.13 ek: 6,75EUR | Male speedwell wort, ... | 274239         | 1       |
| AHD                       | Bitter fennel            | 15006502       | 1       |
| AHD                       | Sodium hydrogen carbo... | 1208008-01     | 13      |
| AHD                       | Sodium monohydrogenph... | 112345013      | 1       |
| AHD                       | Tragacanth, powdered     | 15379906       | 2       |
| AHD 10.02.17 EK.3,50      | Aniseed                  | 16200801       | 1       |
| Akazie                    | Black cumin seed         | 20.09.2015     | 1       |
| Akazie                    | Cinnamon, cut            | 20.09.2015     | 1       |
| Akazie                    | Dill fruit               | 20.09.2015     | 1       |
| Akazie                    | Linseed                  | 20.09.2015     | 2       |
| Akazie                    | Rosemary leaf, cut       | 20.09.2015     | 1       |
| Akazien-Apo               | Cinnamon, cut            | Test           | 1       |
| Aldrich                   | Sodium propionate        | U02796-056     | 1       |
| Alfred Galke              | Alchemilla, cut          | 20921          | 1       |
| Alfred Galke              | Bitter fennel            | 18270          | 1       |
| Alfred Galke              | Caraway fruit            | 20069          | 1       |
| Alfred Galke              | Melissa leaf, cut        | D-NI-1-9516-BC | 1       |
| Alfred Galke              | Raspberry leaf, cut      | 19851          | 1       |
| Alfred Galke              | Shepherd's purse, cut    | 20591          | 1       |
| Alfred Galke              | Yarrow herb, cut         | 19861          | 1       |
| Alliance                  | Hawthorn flower          | 13010403       | 1       |
| Alliance                  | Heather, cut             | 255389         | 1       |
| Alliance                  | Robert herb, cut         | 3951A110621    | 6       |
| Alliance                  | Sodium monohydrogenph... | 12256606       | 1       |
| Alliance Health           | Aluminium potassium s... | 13025401       | 3       |
| Alliance healthcare       | Sodium monohydrogenph... | 12L05-N04      | 2       |
| Alliance Healthcare       | Aluminium potassium s... | 13025404       | 1       |
| Alte Apotheke             | Oak bark, cut            | 15314904       | 2       |
| an                        | Blessed thistle, cut     | 13389704       | 1       |
| an                        | Gentian root, cut        | 6311b130305    | 1       |
| an                        | Hawthorn leaf with fl... | 1971A130930    | 2       |
| an                        | Passionflower herb, cut  | 13141212       | 1       |
| an                        | Raspberry leaf, cut      | 13086708       | 1       |
| an                        | Roselle                  | 14018101       | 1       |
| an                        | Verbena herb, cut        | 12383007       | 1       |
| Anzag                     | Acorus root, natural,... | 276260         | 3       |
| Anzag                     | Aluminium chloride he... | 1109025-01     | 6       |
| Anzag                     | Aluminium potassium s... | 1218441        | 1       |
| Anzag                     | Angelica root            | 12168703       | 3       |
| Anzag                     | Blessed thistle, cut     | 271946         | 1       |
| Anzag                     | Blessed thistle, cut     | 282281         | 1       |
| Anzag                     | Calendula flower, cut    | 12221706       | 16      |
| Anzag                     | Centaury, cut            | 2727897        | 1       |
| Anzag                     | Cowberry extract 6:1     | 20206/01       | 1       |
| Anzag                     | Damiana leaf, cut        | 11026606       | 1       |
| Anzag                     | Dandelion herb with r... | 274030         | 1       |

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| Supplier                  | Substance                | Batch          | Spectra |
|---------------------------|--------------------------|----------------|---------|
| Anzag                     | Ispaghula seed           | 11185818       | 1       |
| Anzag                     | Lavender flower          | 1488A12803     | 1       |
| Anzag                     | Lime flower, cut         | 7120           | 1       |
| Anzag                     | Linseed                  | 12137105       | 1       |
| Anzag                     | Liquorice root, peeled   | 272896         | 1       |
| Anzag                     | Magnesium chloride he... | 1304003-01     | 2       |
| Anzag                     | Magnesium chloride he... | 120802501      | 1       |
| Anzag                     | Magnesium chloride he... | 111201301      | 1       |
| Anzag                     | Maize style, cut         | 274920         | 1       |
| Anzag                     | Marian thistle fruit     | 11126702       | 12      |
| Anzag                     | Marshmallow root, pee... | 11126702       | 1       |
| Anzag                     | Meadowsweet herb, cut    | 10381602       | 5       |
| Anzag                     | Mullein flower, cut      | 11020714       | 5       |
| Anzag                     | Nettle leaf, cut         | 2381-A130122   | 1       |
| Anzag                     | Nystatin                 | 2902041-02     | 1       |
| Anzag                     | Passionflower herb, cut  | 1207211669     | 1       |
| Anzag                     | Ramsons herb, cut        | 11182207       | 2       |
| Anzag                     | Robert herb, cut         | 11147806       | 1       |
| Anzag                     | Star anise               | 10376403       | 5       |
| Anzag                     | Sweet woodruff herb, ... | 12103504       | 2       |
| Anzag                     | Trichloroacetic acid     | 12135204       | 5       |
| Anzag                     | Walnut bark, cut         | 711B110128     | 3       |
| Anzag                     | White deadnettle herb... | 11010606       | 1       |
| Anzag                     | Yarrow herb, cut         | 11306307       | 1       |
| ANZAG                     | Walnut leaf, cut         | 12124603       | 16      |
| Anzag 05.10.2012          | Coltsfoot leaf, cut      | 121005         | 2       |
| Anzag 06.04.2016          | Aniseed                  | 15398601       | 1       |
| Anzag 07.11.12            | Liquorice root, peeled   | 11034018       | 1       |
| Anzag 07.11.12 ek: 2,48   | Aluminium potassium s... | 12184402       | 5       |
| Anzag 10.05 2010          | Hawthorn leaf with fl... | 1910E-01485    | 1       |
| Anzag 10.05.13 ek:3,16EUR | Dandelion herb with r... | 6611B130321    | 1       |
| Anzag 11.09.2012          | Calcium hydroxide        | 112F08-N02     | 1       |
| Anzag 12.03.13 ek: 4,...  | St. John's wort, cut     | 11185608       | 2       |
| Anzag 12.11.12 ek:11,04   | Lime flower, cut         | 1611B120827    | 14      |
| Anzag 12.11.12 ek:3,85    | Yarrow herb, cut         | 11280513       | 1       |
| Anzag 13.02.13 ek: 4,...  | Magnesium sulfate, dr... | 11265910       | 1       |
| Anzag 13.12.12 ek: 5,...  | Calendula flower, cut    | 1241C120321    | 5       |
| Anzag 14.03.13 ek:6,60EUR | Marshmallow root, pee... | 6071A130116    | 12      |
| Anzag 17.04.13 ek: 2,...  | Tall golden rod, cut     | 4521A110816    | 2       |
| Anzag 17.07.2012          | Dithranole               | APDT/365/2011D | 3       |
| Anzag 19.09.2012          | White mustard seed, p... | 11114409       | 2       |
| Anzag 22.03.13 ek: 5,...  | Aloes, cape, powdered    | 12232102       | 1       |
| Anzag 25.10.12 ek:3.16EUR | Dandelion herb with r... | 6611B110131    | 1       |
| Anzag 26.02.13 ek: 10...  | Willowherb, small flo... | 4721C120321    | 17      |
| Anzag 26.10.12 2.36EUR    | Oak bark, cut            | 10348616       | 7       |
| Anzag 27.12.12 ek:2,79    | Blackberry leaf, cut     | 10136048       | 1       |
| Anzag 28.08.2012          | Bilberry fruit, dried    | 10273712       | 2       |
| Anzag 28.08.2012          | Daisy flower             | 11068306       | 1       |
| Anzag 28.08.2012          | Dandelion root, cut      | 11003311       | 3       |
| Anzag 29.04.13 ek: 4,...  | Magnesium sulfate hep... | 12138518       | 4       |
| Anzag 6.03.13 ek: 13...   | Matricaria flower        | 12244805       | 5       |
| anzag 8.8.13              | Nettle leaf, cut         | 12183901       | 3       |
| Anzag am 05.05.2012       | Marshmallow root, pee... | 11101809       | 2       |
| ANZAG am 06.06.2012       | Rosemary leaf, cut       | 268132         | 4       |
| Anzag am 08.05.2012       | Aluminium chloride he... | 12C07-N01      | 15      |
| Anzag am 08.05.2012       | Motherwort herb, cut     | 10244612       | 1       |
| ANZAG am 15.05.2012       | Aluminium potassium s... | 1108049-01     | 4       |
| ANZAG am 15.05.2012       | Ladys bedstraw herb,...  | 10375704       | 2       |
| ANZAG am 22.05.2012       | Aluminium potassium s... | 12022401       | 2       |
| ANZAG am 22.05.2012       | Raspberry leaf, cut      | 2291A111124    | 3       |

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| Supplier                   | Substance                | Batch          | Spectra |
|----------------------------|--------------------------|----------------|---------|
| ANZAG am 23.05.2012        | Calcium hydrogen phos... | 10135228       | 2       |
| ANZAG am 23.05.2012        | Common wormwood herb,... | 11286301       | 1       |
| ANZAG am 23.05.2012        | Potassium hydrocarbon... | 11105811       | 4       |
| ANZAG am 23.05.2012        | Rosemary leaf, cut       | 2261A100916    | 1       |
| Anzag am 24.04.2012        | Fumitory, cut            | 3881B100127    | 3       |
| Anzag am 24.05.2012        | Sodium hydrogen carbo... | 11E31-N04      | 1       |
| Anzag ek: 2,59EUR 19.09... | Caraway fruit            | 11003216       | 4       |
| Anzag ek: 4,58EUR 25.09... | Walnut leaf, cut         | 2111A120123    | 9       |
| Anzag ek: 4,88EUR 26.09... | Male speedwell wort, ... | 4661C120321    | 11      |
| Anzag ek: 6,39 11,09...    | Alchemilla, cut          | 11182806       | 9       |
| Anzag ek:2,64EUR 16.07.12  | Mistletoe, cut           | 10273417       | 1       |
| Anzag ek:3,13EUR 15.09.12  | Melilot herb, cut        | 11307605       | 5       |
| Anzag ek:8,77EUR 30.08.12  | Manna, cut               | 11308904       | 5       |
| Anzag EK7,91 08.08.12      | Gentian root, cut        | 10263407       | 1       |
| Anzag, 18.05.2012          | Birch leaf, cut          | 259195         | 1       |
| Anzag, 18.07.2012          | Yarrow herb, cut         | 11106405       | 1       |
| Anzag, 24.10.2012          | Yarrow herb, cut         | 270116         | 2       |
| anzag, 31.10.2012          | Lavender flower          |                | 1       |
| anzag,26.11.12             | Ammonium hydrogen car... | 12022308       | 5       |
| Anzag/                     | Dithranole               | APDT3652011    | 1       |
| Anzag/                     | Robert herb, cut         | 11147813       | 5       |
| Apofit                     | Fenugreek                | 222392         | 1       |
| ApoFit/Noweda              | Walnut leaf, cut         | 271137         | 1       |
| Apomix                     | Trichloroacetic acid     | 12G04-M11      | 1       |
| Apomix / 11                | Carbachol                | 12330703       | 1       |
| apomix/Phönix              | Oak bark, cut            | 9357419        | 2       |
| Apotheke Bühlau            | Almonds, bitter, whole   | 267467         | 2       |
| Apotheke Bühlau            | Horse chestnut leaf, ... | 100416         | 1       |
| Audor Pharma               | Dithranole               | APDT/365/2011  | 4       |
| Audor Pharma               | Dithranole               | DT/351/2010D   | 1       |
| Audor Pharma               | Dithranole               | APDT/365/2011/ | 1       |
| Audor Pharma               | Dithranole               | APDT/351/2010D | 1       |
| Audor Pharma               | Dithranole               | APDT/386/2012D | 1       |
| Audor Pharma               | Dithranole               | APDT3752012D   | 3       |
| Audor Pharma               | Dithranole               | APDT3902013D   | 1       |
| Audor Pharma               | Dithranole               | DT/365/2011D   | 1       |
| Audor Pharma               | Dithranole               | ApDt/365/2011D | 1       |
| Audor Pharma               | Nystatin                 | 11C07-N05N     | 1       |
| Audor Pharma               | Nystatin                 | AP11K11-N04N   | 1       |
| Audor Pharma               | Nystatin                 | AP11G07-N12N   | 1       |
| Aurica                     | Aniseed                  | 521302895      | 1       |
| Aurica                     | Birch leaf, cut          | 521205644      | 1       |
| Aurica                     | Common wormwood herb,... | 521305386      | 1       |
| Aurica                     | Dandelion herb with r... | 521200197      | 1       |
| Aurica                     | Equisetum stem, cut      | 521205308      | 1       |
| Aurica                     | Nettle leaf, cut         | 224131         | 1       |
| Aurica                     | Passionflower herb, cut  | 521300655      | 1       |
| Aurica                     | Red clover flower        | 521203442      | 1       |
| Aurica                     | Red clover flower        | 521206331      | 1       |
| Aurica                     | Rose hips with peel, ... | 521201801      | 1       |
| Aurica                     | Sage leaf, cut           | 521204613      | 1       |
| Aurica                     | St. John's wort, cut     | 521202559      | 1       |
| Aurica                     | St. John's wort, cut     | 521200778      | 1       |
| Aurica                     | Tall golden rod, cut     | 521201267      | 1       |
| Aurica                     | Tall golden rod, cut     | 224133         | 2       |
| Aurica                     | Thyme, rubbed            | 521207003      | 1       |
| Aurica                     | Valerian root, cut       | 221838         | 2       |
| Aurica                     | Verbena herb, cut        | 521305668      | 1       |
| Aurica / 11                | Equisetum stem, cut      | 521302898      | 1       |
| Aurica / 11                | Juniper                  | 521301390      | 1       |

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| Supplier                 | Substance                | Batch     | Spectra |
|--------------------------|--------------------------|-----------|---------|
| Aurica / 11              | Primrose flower          | 521301234 | 1       |
| Aurica Naturheilmitte... | Aniseed, powdered        | 521405796 | 1       |
| Aurica Naturheilmitte... | Aniseed                  | 521600679 | 1       |
| Aurica/ Noweda           | St. John's wort, cut     | 521305424 | 1       |
| Aurica/ Sanacorp         | Thyme, rubbed            | 521301852 | 1       |
| Aurica/ Vedono           | Peppermint leaf, cut     | 521301217 | 1       |
| Aurica/ Anzag            | Red clover flower        | 521303918 | 1       |
| Aurica/ Gehe             | Primrose flower          | 521203308 | 1       |
| aurica/phoenix           | Liquorice root, natur... | 521206925 | 1       |
| Aurica/ Phönix           | Acorus root, peeled      | 150649    | 1       |
| Aurica/ Phönix           | Angelica root            | 520800638 | 1       |
| Aurica/ Phönix           | Bean shells, cut         | 5052301   | 1       |
| Aurica/ Phönix           | Centaury, cut            | 520702152 | 1       |
| Aurica/ Phönix           | Juniper                  | 521006043 | 1       |
| Aurica/ Phönix           | Maize style, cut         | 520901387 | 1       |
| Aurica/ Phönix           | Male speedwell wort, ... | 520708362 | 1       |
| Aurica/ Phönix           | Mistletoe, cut           | 6110801   | 1       |
| Bahnhof-Apotheke         | Acorus root, peeled      | 17-121107 | 1       |
| Bahnhof-Apotheke         | Alchemilla, cut          | 17-121107 | 1       |
| Bahnhof-Apotheke         | Aniseed                  | 7-120913  | 1       |
| Bahnhof-Apotheke         | Birch leaf, cut          | 18-120702 | 1       |
| Bahnhof-Apotheke         | Bitter fennel            | 11-121029 | 1       |
| Bahnhof-Apotheke         | Blackberry leaf, cut     | 18-120702 | 1       |
| Bahnhof-Apotheke         | Calendula flower, cut    | 17-121106 | 1       |
| Bahnhof-Apotheke         | Caraway fruit            | 18-120709 | 1       |
| Bahnhof-Apotheke         | Elder flower, rubbed     | 17-121112 | 1       |
| Bahnhof-Apotheke         | Hawthorn leaf with fl... | 7-121011  | 1       |
| Bahnhof-Apotheke         | Hay flower               | 13-121105 | 1       |
| Bahnhof-Apotheke         | Lime flower, cut         | 7-121011  | 1       |
| Bahnhof-Apotheke         | Liquorice root, peeled   | 17-121112 | 1       |
| Bahnhof-Apotheke         | Lycopodium herb, cut     | 17-121112 | 1       |
| Bahnhof-Apotheke         | Maize style, cut         | 20-121018 | 1       |
| Bahnhof-Apotheke         | Male speedwell wort, ... | 4-121002  | 1       |
| Bahnhof-Apotheke         | Matricaria flower        | 11-121024 | 1       |
| Bahnhof-Apotheke         | Melissa leaf, cut        | 17-120917 | 1       |
| Bahnhof-Apotheke         | Nettle leaf, cut         | 7-121109  | 1       |
| Bahnhof-Apotheke         | Oak bark, cut            | 17-121106 | 1       |
| Bahnhof-Apotheke         | Psyllium seed            | 3-121005  | 1       |
| Bahnhof-Apotheke         | Raspberry leaf, cut      | 17-120917 | 1       |
| Bahnhof-Apotheke         | Ribwort plantain, cut    | 7-121011  | 1       |
| Bahnhof-Apotheke         | Rosemary leaf, cut       | 7-120915  | 1       |
| Bahnhof-Apotheke         | Sage leaf, cut           | 3-121018  | 1       |
| Bahnhof-Apotheke         | Shepherd's purse, cut    | 4-120924  | 1       |
| Bahnhof-Apotheke         | St. John's wort, cut     | 4-121018  | 1       |
| Bahnhof-Apotheke         | Thyme, rubbed            | 17-121112 | 1       |
| Bahnhof-Apotheke         | Willowherb, small flo... | 17-121107 | 1       |
| Bahnhof-Apotheke         | Wormwood herb, cut       | 17-121107 | 1       |
| Bahnhof-Apotheke         | Yarrow herb, cut         | 7-121011  | 1       |
| Berco                    | Maltodextrin             | 1os945-3  | 1       |
| Berkel AHK               | Agnus castus fruit       | 14194401  | 2       |
| Berkel AHK               | Aniseed                  | 13333907  | 11      |
| Berkel AHK               | Aniseed                  | 11374103  | 2       |
| Berkel AHK               | Aniseed                  | 14194401  | 1       |
| Berkel AHK               | Aniseed                  | 13333902  | 10      |
| Berkel AHK               | Aniseed                  | 14110202  | 1       |
| Berkel AHK               | Aniseed                  | 13333912  | 4       |
| Berkel AHK               | Caraway fruit            | 13397103  | 2       |
| Berkel AHK               | Oak bark, cut            | 13011905  | 1       |
| Berkel AHK               | Oak bark, cut            | 13360303  | 5       |
| Berkel AHK               | Oak bark, cut            | 13360310  | 1       |

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| Supplier              | Substance                | Batch        | Spectra |
|-----------------------|--------------------------|--------------|---------|
| Berkel AHK            | Valerian root, powdered  | 13287406     | 1       |
| Berkel AHK            | Valerian root, powdered  | 19196802     | 1       |
| Berkel AHK            | Valerian root, powdered  | 14179403     | 2       |
| BimSiframGroup        | Amygdalin                | STA130512002 | 2       |
| BimSiframGroup        | Amygdalin                | 141120       | 1       |
| BimSiframGroup        | Amygdalin                | 13121802     | 2       |
| Biogenerics           | Amygdalin                | NSIH03040    | 1       |
| BLS                   | Phenobarbital            | 67056        | 1       |
| Bomastus-Werke/Phönix | Rosemary leaf, cut       | 298424       | 2       |
| Bomba/AHD             | Coltsfoot leaf, cut      | 276303       | 6       |
| Bomba/AHD             | Equisetum stem, cut      | 280449       | 4       |
| Bomba/AHD             | Senna leaf, cut          | 280008       | 3       |
| Bomba/AHD             | Tall golden rod, cut     | 279526       | 1       |
| Bomba/AHD             | Willow bark, cut         | 280362       | 1       |
| Bombaltus             | Hop strobile             | 274724       | 1       |
| Bombastus             | Acorus root, natural,... | 281692       | 1       |
| Bombastus             | Acorus root, natural,... | 274159       | 1       |
| Bombastus             | Acorus root, natural,... | 282476       | 1       |
| Bombastus             | Acorus root, natural,... | 277958       | 1       |
| Bombastus             | Acorus root, natural,... | 224114       | 1       |
| Bombastus             | Acorus root, natural,... | 271667       | 1       |
| Bombastus             | Acorus root, natural,... | 273214       | 1       |
| Bombastus             | Acorus root, peeled      | 269479       | 2       |
| Bombastus             | Acorus root, peeled      | 271667       | 1       |
| Bombastus             | Acorus root, peeled      | 274159       | 3       |
| Bombastus             | Acorus root, peeled      | 267365       | 1       |
| Bombastus             | Alchemilla alpina her... | 278889       | 1       |
| Bombastus             | Alchemilla, cut          | 276173       | 4       |
| Bombastus             | Alchemilla, cut          | 14066007     | 1       |
| Bombastus             | Alchemilla, cut          | 268287       | 1       |
| Bombastus             | Alchemilla, cut          | 521203995    | 1       |
| Bombastus             | Alchemilla, cut          | 278889       | 3       |
| Bombastus             | Alchemilla, cut          | 263194       | 1       |
| Bombastus             | Alchemilla, cut          | 231013B      | 1       |
| Bombastus             | Alchemilla, cut          | 282032       | 2       |
| Bombastus             | Alchemilla, cut          | 279070       | 6       |
| Bombastus             | Alchemilla, cut          | 264972       | 2       |
| Bombastus             | Alchemilla, cut          | 272021       | 5       |
| Bombastus             | Almonds, bitter, whole   | 305322       | 1       |
| Bombastus             | Almonds, bitter, whole   | 267529       | 1       |
| Bombastus             | Almonds, bitter, whole   | 275601       | 1       |
| Bombastus             | Almonds, bitter, whole   | 283369       | 1       |
| Bombastus             | Almonds, bitter, whole   | 303218       | 2       |
| Bombastus             | Almonds, bitter, whole   | 284978       | 1       |
| Bombastus             | Almonds, bitter, whole   | 275600       | 1       |
| Bombastus             | Almonds, bitter, whole   | 275001       | 3       |
| Bombastus             | Almonds, bitter, whole   | 290973       | 4       |
| Bombastus             | Angelica root            | 284545       | 1       |
| Bombastus             | Angelica root            | 272895       | 1       |
| Bombastus             | Angelica root            | 281280       | 7       |
| Bombastus             | Angelica root            | 283387       | 1       |
| Bombastus             | Angelica root            | 270117       | 2       |
| Bombastus             | Angelica root            | 285732       | 2       |
| Bombastus             | Angelica root            | 218280       | 1       |
| Bombastus             | Angelica root            | 290309       | 1       |
| Bombastus             | Angelica root            | 291848       | 1       |
| Bombastus             | Angelica root            | 295085       | 2       |
| Bombastus             | Angelica root            | 307041       | 1       |
| Bombastus             | Angelica root            | 305460       | 1       |
| Bombastus             | Angelica root            | 278294       | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b> | <b>Spectra</b> |
|-----------------|--------------------------|--------------|----------------|
| Bombastus       | Angelica root            | 277310       | 4              |
| Bombastus       | Angelica root            | 275878       | 1              |
| Bombastus       | Angelica root            | 272954       | 4              |
| Bombastus       | Angelica root            | 275879       | 1              |
| Bombastus       | Angelica root            | 301768       | 1              |
| Bombastus       | Angelica root            | 301767       | 1              |
| Bombastus       | Aniseed                  | 268180       | 1              |
| Bombastus       | Aniseed                  | 273682       | 2              |
| Bombastus       | Aniseed                  | 276456       | 1              |
| Bombastus       | Aniseed                  | 278925       | 2              |
| Bombastus       | Aniseed                  | 282917       | 2              |
| Bombastus       | Aniseed                  | 285777       | 1              |
| Bombastus       | Aniseed                  | 285778       | 2              |
| Bombastus       | Aniseed                  | 289846       | 1              |
| Bombastus       | Arnica flower            | 271581       | 2              |
| Bombastus       | Arnica flower            | 271668       | 1              |
| Bombastus       | Arnica flower            | 280672       | 1              |
| Bombastus       | Artichoke leaf, cut      | 8202213593   | 1              |
| Bombastus       | Bean shells, cut         | 272781       | 5              |
| Bombastus       | Bean shells, cut         | 270517       | 2              |
| Bombastus       | Bean shells, cut         | 240503       | 1              |
| Bombastus       | Bean shells, cut         | 278686       | 1              |
| Bombastus       | Bean shells, cut         | 278696       | 3              |
| Bombastus       | Bean shells, cut         | 282475       | 1              |
| Bombastus       | Bearberry leaf, cut      | 272297       | 8              |
| Bombastus       | Bearberry leaf, cut      | 275491       | 3              |
| Bombastus       | Bilberry leaf, cut       | 273581       | 2              |
| Bombastus       | Bilberry leaf, cut       | 283170       | 1              |
| Bombastus       | Bilberry leaf, cut       | 272176       | 3              |
| Bombastus       | Birch leaf, cut          | 287280       | 1              |
| Bombastus       | Birch leaf, cut          | 278316       | 1              |
| Bombastus       | Birch leaf, cut          | 277822       | 2              |
| Bombastus       | Birch leaf, cut          | 274499       | 2              |
| Bombastus       | Birch leaf, cut          | 274498       | 1              |
| Bombastus       | Birch leaf, cut          | 272385       | 1              |
| Bombastus       | Birch leaf, cut          | 270743       | 1              |
| Bombastus       | Birch leaf, cut          | 266623       | 2              |
| Bombastus       | Birch leaf, cut          | 280677       | 1              |
| Bombastus       | Birch leaf, cut          | 267077       | 2              |
| Bombastus       | Birch leaf, cut          | 269195       | 1              |
| Bombastus       | Bitter fennel            | 267683       | 1              |
| Bombastus       | Bitter fennel            | 299385       | 1              |
| Bombastus       | Bitter fennel            | 280891       | 2              |
| Bombastus       | Bitter fennel            | 289870       | 1              |
| Bombastus       | Bitter fennel            | 275922       | 5              |
| Bombastus       | Bitter fennel            | 289869       | 1              |
| Bombastus       | Bitter fennel            | 296877       | 1              |
| Bombastus       | Bitter fennel            | 285609       | 1              |
| Bombastus       | Bitter fennel            | 289870       | 2              |
| Bombastus       | Bitter fennel            | 268130       | 4              |
| Bombastus       | Bitter fennel            | 293627       | 1              |
| Bombastus       | Bitter fennel            | 275921       | 1              |
| Bombastus       | Bitter fennel            | 273706       | 5              |
| Bombastus       | Bitter orange peel, cut  | 278233       | 4              |
| Bombastus       | Bitter orange peel, cut  | 267364       | 1              |
| Bombastus       | Bitter orange peel, cut  | 274240       | 5              |
| Bombastus       | Blackberry leaf, cut     | 273668       | 3              |
| Bombastus       | Blackberry leaf, cut     | 261490       | 1              |
| Bombastus       | Blackberry leaf, cut     | 267122       | 3              |
| Bombastus       | Blue bottle flower wi... | 275759       | 2              |

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| Supplier  | Substance                  | Batch             | Spectra |
|-----------|----------------------------|-------------------|---------|
| Bombastus | Blue bottle flower wi. . . | 284030            | 1       |
| Bombastus | Calendula flower           | 279632            | 1       |
| Bombastus | Calendula flower           | 280306            | 2       |
| Bombastus | Calendula flower           | 268626            | 1       |
| Bombastus | Calendula flower, cut      | 270046            | 5       |
| Bombastus | Calendula flower, cut      | 275128            | 1       |
| Bombastus | Calendula flower, cut      | 234997            | 1       |
| Bombastus | Calendula flower, cut      | 253620            | 1       |
| Bombastus | Calendula flower, cut      | 261332            | 1       |
| Bombastus | Calendula flower, cut      | 207294            | 1       |
| Bombastus | Calendula flower, cut      | 279632            | 1       |
| Bombastus | Calendula flower, cut      | 275813            | 1       |
| Bombastus | Caraway fruit              | 277491            | 2       |
| Bombastus | Caraway fruit              | 282269            | 1       |
| Bombastus | Caraway fruit              | 270278            | 1       |
| Bombastus | Caraway fruit              | 272730            | 1       |
| Bombastus | Caraway fruit              | 275849            | 2       |
| Bombastus | Caraway fruit              | 270124            | 1       |
| Bombastus | Caraway fruit              | 275228            | 1       |
| Bombastus | Centaury, cut              | 262982            | 2       |
| Bombastus | Centaury, cut              | 281951            | 1       |
| Bombastus | Centaury, cut              | 277598            | 3       |
| Bombastus | Coltsfoot leaf, cut        | 274289            | 6       |
| Bombastus | Coltsfoot leaf, cut        | 285263            | 3       |
| Bombastus | Coltsfoot leaf, cut        | 275489            | 3       |
| Bombastus | Coltsfoot leaf, cut        | 281100            | 4       |
| Bombastus | Coltsfoot leaf, cut        | 26693             | 1       |
| Bombastus | Coltsfoot leaf, cut        | 269501            | 5       |
| Bombastus | Coltsfoot leaf, cut        | 272019            | 1       |
| Bombastus | Coltsfoot leaf, cut        | 266999            | 1       |
| Bombastus | Coltsfoot leaf, cut        | 265856            | 1       |
| Bombastus | Coltsfoot leaf, cut        | 232339            | 1       |
| Bombastus | Coltsfoot leaf, cut        | 266691            | 2       |
| Bombastus | Coltsfoot leaf, cut        | 277131            | 1       |
| Bombastus | Coltsfoot leaf, cut        | 277848            | 2       |
| Bombastus | Coltsfoot leaf, cut        | 278758            | 7       |
| Bombastus | Comfrey herb, cut          | 281531            | 1       |
| Bombastus | Coriander                  | 263733            | 1       |
| Bombastus | Couch grass rhizome, ...   | 262175            | 1       |
| Bombastus | Couch grass rhizome, ...   | 276777            | 4       |
| Bombastus | Couch grass rhizome, ...   | 269196            | 1       |
| Bombastus | Couch grass rhizome, ...   | 270500            | 2       |
| Bombastus | Couch grass rhizome, ...   | 273387            | 4       |
| Bombastus | Dandelion herb with r...   | 264967            | 1       |
| Bombastus | Dandelion herb with r...   | 280363-3385310110 | 1       |
| Bombastus | Dandelion herb with r...   | 274030            | 4       |
| Bombastus | Dandelion herb with r...   | 258809            | 1       |
| Bombastus | Dandelion herb with r...   | 271272            | 5       |
| Bombastus | Dandelion herb with r...   | 275126            | 3       |
| Bombastus | Dandelion herb with r...   | 282916            | 7       |
| Bombastus | Dandelion herb with r...   | 285264            | 1       |
| Bombastus | Dandelion herb with r...   | 280363            | 6       |
| Bombastus | Dandelion herb with r...   | 290125            | 1       |
| Bombastus | Dandelion herb with r...   | 277597            | 8       |
| Bombastus | Dandelion herb withou...   | 11371901          | 1       |
| Bombastus | Dandelion herb withou...   | 11371906          | 2       |
| Bombastus | Dill herb, cut             | 50836505          | 1       |
| Bombastus | Elder flower, rubbed       | 265631            | 1       |
| Bombastus | Elder flower, rubbed       | 275393            | 5       |
| Bombastus | Elder flower, rubbed       | 269873            | 3       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b> | <b>Spectra</b> |
|-----------------|--------------------------|--------------|----------------|
| Bombastus       | Elder flower, rubbed     | 279216       | 9              |
| Bombastus       | Equisetum stem, cut      | 264100       | 1              |
| Bombastus       | Equisetum stem, cut      | 268321       | 1              |
| Bombastus       | Equisetum stem, cut      | 278107       | 1              |
| Bombastus       | Equisetum stem, cut      | 266865       | 1              |
| Bombastus       | Equisetum stem, cut      | 275891       | 3              |
| Bombastus       | Equisetum stem, cut      | 275836       | 2              |
| Bombastus       | Equisetum stem, cut      | 274714       | 1              |
| Bombastus       | Equisetum stem, cut      | 6011401      | 1              |
| Bombastus       | Equisetum stem, cut      | 274168       | 1              |
| Bombastus       | Equisetum stem, cut      | 279133       | 2              |
| Bombastus       | Equisetum stem, cut      | 273963       | 2              |
| Bombastus       | Equisetum stem, cut      | 272552       | 3              |
| Bombastus       | Equisetum stem, cut      | 269031       | 2              |
| Bombastus       | Equisetum stem, cut      | 268534       | 2              |
| Bombastus       | Equisetum stem, cut      | 265924       | 1              |
| Bombastus       | Equisetum stem, cut      | 18111304     | 1              |
| Bombastus       | Equisetum stem, cut      | 264101       | 1              |
| Bombastus       | Equisetum stem, cut      | 280647       | 1              |
| Bombastus       | Euphrasy herb, cut       | 277846       | 1              |
| Bombastus       | Euphrasy herb, cut       | 274553       | 1              |
| Bombastus       | Euphrasy herb, cut       | 278108       | 2              |
| Bombastus       | Frangula bark, cut       | 275998       | 4              |
| Bombastus       | Frangula bark, cut       | 278599       | 4              |
| Bombastus       | Frangula bark, cut       | 273926       | 1              |
| Bombastus       | Frangula bark, cut       | 270733       | 1              |
| Bombastus       | Frangula bark, cut       | 238812       | 1              |
| Bombastus       | Frangula bark, cut       | 268407       | 4              |
| Bombastus       | Frangula bark, cut       | 249091       | 2              |
| Bombastus       | Frangula bark, cut       | 281284       | 2              |
| Bombastus       | Ginseng root             | 13150903     | 1              |
| Bombastus       | Hawthorn leaf with fl... | 275309       | 3              |
| Bombastus       | Hawthorn leaf with fl... | 272881       | 1              |
| Bombastus       | Hawthorn leaf with fl... | 272177       | 1              |
| Bombastus       | Hawthorn leaf with fl... | 267000       | 1              |
| Bombastus       | Hawthorn leaf with fl... | 264044       | 1              |
| Bombastus       | Hawthorn leaf with fl... | 275310       | 2              |
| Bombastus       | Hawthorn leaf with fl... | 267551       | 1              |
| Bombastus       | Hawthorn leaf with fl... | 265197       | 2              |
| Bombastus       | Hawthorn leaf with fl... | 267551       | 2              |
| Bombastus       | Hawthorn leaf with fl... | 282220       | 1              |
| Bombastus       | Hawthorn leaf with fl... | 278756       | 1              |
| Bombastus       | Hawthorn leaf with fl... | 273287       | 1              |
| Bombastus       | Heather, cut             | 278314       | 2              |
| Bombastus       | Hop strobile             | 277821       | 2              |
| Bombastus       | Hop strobile             | 276976       | 1              |
| Bombastus       | Hop strobile             | 10240403     | 1              |
| Bombastus       | Hop strobile             | 208502       | 1              |
| Bombastus       | Hop strobile             | 271870       | 2              |
| Bombastus       | Iceland moss, cut        | 12187108     | 4              |
| Bombastus       | Iceland moss, cut        | 13357802     | 1              |
| Bombastus       | Ladys bedstraw herb,...  | 3921B120130  | 1              |
| Bombastus       | Lavender flower          | 276799       | 2              |
| Bombastus       | Lavender flower          | 268831       | 2              |
| Bombastus       | Lavender flower          | 274469       | 1              |
| Bombastus       | Lime flower, cut         | 266863       | 1              |
| Bombastus       | Lime flower, cut         | 276813       | 1              |
| Bombastus       | Lime flower, cut         | 280678       | 3              |
| Bombastus       | Lime flower, cut         | 281042       | 1              |
| Bombastus       | Lime flower, cut         | 267693       | 1              |

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| Supplier  | Substance                | Batch       | Spectra |
|-----------|--------------------------|-------------|---------|
| Bombastus | Lime flower, cut         | 25091205    | 1       |
| Bombastus | Lime flower, cut         | 268477      | 2       |
| Bombastus | Lime flower, cut         | 275129      | 3       |
| Bombastus | Linseed                  | 282734      | 3       |
| Bombastus | Linseed                  | 278457      | 6       |
| Bombastus | Linseed                  | 1610        | 1       |
| Bombastus | Linseed                  | 269500      | 1       |
| Bombastus | Linseed                  | 295376      | 1       |
| Bombastus | Linseed                  | 274032      | 1       |
| Bombastus | Liquorice root, peeled   | 270192      | 1       |
| Bombastus | Liquorice root, peeled   | 270853      | 5       |
| Bombastus | Liquorice root, peeled   | 268001      | 1       |
| Bombastus | Liquorice root, natur... | 286584      | 1       |
| Bombastus | Liquorice root, natur... | 2901312151  | 1       |
| Bombastus | Liquorice root, natur... | 5091305     | 1       |
| Bombastus | Liquorice root, natur... | 267852      | 2       |
| Bombastus | Liquorice root, natur... | 903312151   | 1       |
| Bombastus | Liquorice root, natur... | 278377      | 5       |
| Bombastus | Liquorice root, natur... | 3713Q2151   | 1       |
| Bombastus | Liquorice root, natur... | 284243      | 3       |
| Bombastus | Liquorice root, natur... | 274921      | 4       |
| Bombastus | Liquorice root, natur... | 276468      | 6       |
| Bombastus | Liquorice root, natur... | 285185      | 2       |
| Bombastus | Liquorice root, natur... | 279409      | 2       |
| Bombastus | Lovage root, cut         | 273001      | 1       |
| Bombastus | Lovage root, cut         | 260409      | 1       |
| Bombastus | Magnesium sulfate hep... | 277424      | 1       |
| Bombastus | Magnesium sulfate hep... | 274794      | 1       |
| Bombastus | Maize style, cut         | 271033      | 1       |
| Bombastus | Maize style, cut         | 276776      | 1       |
| Bombastus | Maize style, cut         | 81113a      | 1       |
| Bombastus | Maize style, cut         | 282574      | 3       |
| Bombastus | Maize style, cut         | 285912      | 1       |
| Bombastus | Male speedwell wort, ... | 278855      | 2       |
| Bombastus | Male speedwell wort, ... | 274238      | 2       |
| Bombastus | Male speedwell wort, ... | 269497      | 2       |
| Bombastus | Male speedwell wort, ... | 268409      | 1       |
| Bombastus | Male speedwell wort, ... | 265564      | 1       |
| Bombastus | Mallow flower, cut       | 13267304    | 1       |
| Bombastus | Mallow leaf, cut         | 273803      | 1       |
| Bombastus | Mallow leaf, cut         | 267168      | 3       |
| Bombastus | Mallow leaf, cut         | 272034      | 2       |
| Bombastus | Mallow leaf, cut         | 278925      | 2       |
| Bombastus | Marian thistle fruit     | 13122013a   | 1       |
| Bombastus | Marian thistle fruit     | 262426      | 1       |
| Bombastus | Marian thistle fruit     | 268192      | 1       |
| Bombastus | Marian thistle fruit     | 278379      | 1       |
| Bombastus | Marian thistle fruit     | 272575      | 1       |
| Bombastus | Marian thistle fruit     | 277720      | 3       |
| Bombastus | Marian thistle fruit     | 278378      | 1       |
| Bombastus | Marian thistle fruit     | 284420      | 1       |
| Bombastus | Marian thistle fruit     | 296193      | 1       |
| Bombastus | Marian thistle fruit     | 296535      | 1       |
| Bombastus | Marian thistle fruit     | 299483      | 1       |
| Bombastus | Marian thistle fruit     | 7180A110209 | 4       |
| Bombastus | Marian thistle fruit     | 269499      | 1       |
| Bombastus | Marian thistle fruit     | 282034      | 2       |
| Bombastus | Marian thistle fruit     | 279405      | 3       |
| Bombastus | Marshmallow root, nat... | 272130      | 2       |
| Bombastus | Marshmallow root, nat... | 270467      | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>     | <b>Spectra</b> |
|-----------------|--------------------------|------------------|----------------|
| Bombastus       | Marshmallow root, pee... | 273458           | 1              |
| Bombastus       | Matricaria flower        | 268408           | 3              |
| Bombastus       | Matricaria flower        | 280143           | 2              |
| Bombastus       | Matricaria flower        | 283710           | 2              |
| Bombastus       | Matricaria flower        | 287855           | 1              |
| Bombastus       | Matricaria flower        | 277959           | 7              |
| Bombastus       | Matricaria flower        | 276307           | 1              |
| Bombastus       | Matricaria flower        | 274870           | 2              |
| Bombastus       | Matricaria flower        | 299185           | 1              |
| Bombastus       | Matricaria flower        | 271781           | 5              |
| Bombastus       | Matricaria flower        | 262364           | 2              |
| Bombastus       | Matricaria flower        | 266864           | 1              |
| Bombastus       | Matricaria flower        | 274106           | 3              |
| Bombastus       | Matricaria flower        | 264997           | 1              |
| Bombastus       | Matricaria flower        | 277997           | 2              |
| Bombastus       | Matricaria flower        | 278414           | 2              |
| Bombastus       | Matricaria flower        | 270579           | 4              |
| Bombastus       | Matricaria flower        | 273388           | 3              |
| Bombastus       | Matricaria flower        | 273667           | 2              |
| Bombastus       | Matricaria flower        | 274105           | 1              |
| Bombastus       | Matricaria flower        | 268712           | 1              |
| Bombastus       | Melissa leaf, cut        | 261988           | 1              |
| Bombastus       | Melissa leaf, cut        | 270044           | 2              |
| Bombastus       | Melissa leaf, cut        | 266341           | 1              |
| Bombastus       | Melissa leaf, cut        | 273483           | 2              |
| Bombastus       | Melissa leaf, cut        | 273485           | 2              |
| Bombastus       | Melissa leaf, cut        | 276579           | 1              |
| Bombastus       | Melissa leaf, cut        | 277722           | 2              |
| Bombastus       | Melissa leaf, cut        | 271499           | 3              |
| Bombastus       | Methadone hydrochloride  | 13266507         | 2              |
| Bombastus       | Methadone hydrochloride  | 14C24-B01-292858 | 6              |
| Bombastus       | Mistletoe, cut           | 261875           | 2              |
| Bombastus       | Mistletoe, cut           | 277432           | 2              |
| Bombastus       | Mistletoe, cut           | 276155           | 2              |
| Bombastus       | Mistletoe, cut           | 265420           | 1              |
| Bombastus       | Mistletoe, cut           | 271782           | 5              |
| Bombastus       | Nettle leaf, cut         | 260739           | 1              |
| Bombastus       | Nettle leaf, cut         | 266099           | 1              |
| Bombastus       | Nettle leaf, cut         | 255763           | 1              |
| Bombastus       | Nettle leaf, cut         | 270854           | 6              |
| Bombastus       | Nettle leaf, cut         | 270987           | 4              |
| Bombastus       | Nettle leaf, cut         | 272303           | 3              |
| Bombastus       | Nettle leaf, cut         | 273229           | 2              |
| Bombastus       | Nettle leaf, cut         | 275848           | 3              |
| Bombastus       | Nettle leaf, cut         | 275763           | 4              |
| Bombastus       | Nettle leaf, cut         | 277950           | 4              |
| Bombastus       | Nettle leaf, cut         | 266638           | 1              |
| Bombastus       | Nettle leaf, cut         | 267854           | 1              |
| Bombastus       | Nystatin                 | 12158022         | 2              |
| Bombastus       | Oak bark, cut            | 265717           | 1              |
| Bombastus       | Oak bark, cut            | 229090           | 1              |
| Bombastus       | Oak bark, cut            | 264301           | 2              |
| Bombastus       | Oak bark, cut            | 286297           | 1              |
| Bombastus       | Oak bark, cut            | 285327           | 3              |
| Bombastus       | Oak bark, cut            | 274611           | 3              |
| Bombastus       | Oak bark, cut            | 274392           | 3              |
| Bombastus       | Oak bark, cut            | 279525           | 2              |
| Bombastus       | Oak bark, cut            | 272704           | 2              |
| Bombastus       | Olive leaf               | Unbekannt        | 1              |
| Bombastus       | Peppermint leaf, cut     | 270270           | 1              |

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| <b>Supplier</b> | <b>Substance</b>      | <b>Batch</b> | <b>Spectra</b> |
|-----------------|-----------------------|--------------|----------------|
| Bombastus       | Peppermint leaf, cut  | 285914       | 1              |
| Bombastus       | Peppermint leaf, cut  | 282509       | 1              |
| Bombastus       | Peppermint leaf, cut  | 279214       | 1              |
| Bombastus       | Peppermint leaf, cut  | 279634       | 2              |
| Bombastus       | Peppermint leaf, cut  | 275492       | 1              |
| Bombastus       | Peppermint leaf, cut  | 278201       | 2              |
| Bombastus       | Peppermint leaf, cut  | 273843       | 2              |
| Bombastus       | Peppermint leaf, cut  | 272956       | 6              |
| Bombastus       | Peppermint leaf, cut  | 272295       | 1              |
| Bombastus       | Peppermint leaf, cut  | 268379       | 2              |
| Bombastus       | Peppermint leaf, cut  | 267998       | 4              |
| Bombastus       | Peppermint leaf, cut  | 266772       | 2              |
| Bombastus       | Peppermint leaf, cut  | 255719       | 1              |
| Bombastus       | Peppermint leaf, cut  | 246514       | 1              |
| Bombastus       | Peppermint leaf, cut  | 278679       | 3              |
| Bombastus       | Peppermint leaf, cut  | 281282       | 3              |
| Bombastus       | Peppermint leaf, cut  | 276172       | 1              |
| Bombastus       | Peppermint leaf, cut  | 275295       | 4              |
| Bombastus       | Peppermint leaf, cut  | 281043       | 4              |
| Bombastus       | Peppermint leaf, cut  | 271499       | 1              |
| Bombastus       | Peppermint leaf, cut  | 274021       | 2              |
| Bombastus       | Peppermint leaf, cut  | 279914       | 2              |
| Bombastus       | Peppermint leaf, cut  | 278585       | 1              |
| Bombastus       | Raspberry leaf, cut   | 248586       | 1              |
| Bombastus       | Raspberry leaf, cut   | 262836       | 2              |
| Bombastus       | Raspberry leaf, cut   | 272898       | 1              |
| Bombastus       | Raspberry leaf, cut   | 273710       | 7              |
| Bombastus       | Raspberry leaf, cut   | 274507       | 1              |
| Bombastus       | Raspberry leaf, cut   | 269870       | 1              |
| Bombastus       | Raspberry leaf, cut   | 265844       | 1              |
| Bombastus       | Raspberry leaf, cut   | 263050       | 6              |
| Bombastus       | Raspberry leaf, cut   | 273778       | 1              |
| Bombastus       | Raspberry leaf, cut   | 279686       | 3              |
| Bombastus       | Raspberry leaf, cut   | 273668       | 4              |
| Bombastus       | Raspberry leaf, cut   | 267122       | 1              |
| Bombastus       | Raspberry leaf, cut   | 273143       | 2              |
| Bombastus       | Restharrow root, cut  | 274421       | 3              |
| Bombastus       | Restharrow root, cut  | 283708       | 1              |
| Bombastus       | Rhubarb, powdered     | 11043806     | 1              |
| Bombastus       | Ribwort plantain, cut | 263401       | 2              |
| Bombastus       | Ribwort plantain, cut | 279569       | 1              |
| Bombastus       | Ribwort plantain, cut | 278038       | 1              |
| Bombastus       | Ribwort plantain, cut | 276453       | 1              |
| Bombastus       | Ribwort plantain, cut | 275479       | 5              |
| Bombastus       | Ribwort plantain, cut | 270016       | 4              |
| Bombastus       | Rose hips peel, cut   | 283458       | 1              |
| Bombastus       | Rose hips peel, cut   | 277431       | 2              |
| Bombastus       | Rose hips peel, cut   | 285184       | 1              |
| Bombastus       | Rose hips peel, cut   | 269033       | 1              |
| Bombastus       | Rose hips peel, cut   | 231013A      | 1              |
| Bombastus       | Rose hips peel, cut   | 257166       | 1              |
| Bombastus       | Rosemary leaf, cut    | 281843       | 2              |
| Bombastus       | Rosemary leaf, cut    | 277128       | 2              |
| Bombastus       | Rosemary leaf, cut    | 281248       | 1              |
| Bombastus       | Rosemary leaf, cut    | 270171       | 1              |
| Bombastus       | Rosemary leaf, cut    | 272435       | 2              |
| Bombastus       | Sage leaf, cut        | 264390       | 1              |
| Bombastus       | Sage leaf, cut        | 277512       | 1              |
| Bombastus       | Sage leaf, cut        | 275330       | 2              |
| Bombastus       | Sage leaf, cut        | 271253       | 1              |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b> | <b>Spectra</b> |
|-----------------|--------------------------|--------------|----------------|
| Bombastus       | Sage leaf, cut           | 270115       | 1              |
| Bombastus       | Sage leaf, cut           | 255381       | 1              |
| Bombastus       | Sage leaf, cut           | 279929       | 6              |
| Bombastus       | Senna leaf, cut          | 271828       | 1              |
| Bombastus       | Senna leaf, cut          | 275285       | 3              |
| Bombastus       | Senna leaf, cut          | 273474       | 1              |
| Bombastus       | Senna leaf, cut          | 277575       | 4              |
| Bombastus       | Senna leaf, cut          | 266901       | 1              |
| Bombastus       | Senna leaf, cut          | 280581       | 2              |
| Bombastus       | Senna leaf, cut          | 280448       | 2              |
| Bombastus       | Senna leaf, cut          | 273547       | 3              |
| Bombastus       | Senna leaf, cut          | 278109       | 1              |
| Bombastus       | Shepherd's purse, cut    | 12345        | 2              |
| Bombastus       | Shepherd's purse, cut    | 269594       | 6              |
| Bombastus       | Shepherd's purse, cut    | 278856       | 3              |
| Bombastus       | Shepherd's purse, cut    | 284136       | 1              |
| Bombastus       | Shepherd's purse, cut    | 269977       | 1              |
| Bombastus       | Shepherd's purse, cut    | 262668       | 1              |
| Bombastus       | Sodium monohydrogenph... | 11H04-N06    | 1              |
| Bombastus       | St. John's wort, cut     | 268834       | 2              |
| Bombastus       | St. John's wort, cut     | 281530       | 2              |
| Bombastus       | St. John's wort, cut     | 268834       | 3              |
| Bombastus       | St. John's wort, cut     | 265761       | 1              |
| Bombastus       | St. John's wort, cut     | 275106       | 7              |
| Bombastus       | Tall golden rod, cut     | 274290       | 4              |
| Bombastus       | Tall golden rod, cut     | 271459       | 1              |
| Bombastus       | Tall golden rod, cut     | 271460       | 1              |
| Bombastus       | Tall golden rod, cut     | 270047       | 5              |
| Bombastus       | Tall golden rod, cut     | 278697       | 5              |
| Bombastus       | Tall golden rod, cut     | 269563       | 2              |
| Bombastus       | Tall golden rod, cut     | 261756       | 1              |
| Bombastus       | Tall golden rod, cut     | 209974       | 1              |
| Bombastus       | Thyme, rubbed            | 278309       | 2              |
| Bombastus       | Thyme, rubbed            | 243485       | 1              |
| Bombastus       | Thyme, rubbed            | 276508       | 2              |
| Bombastus       | Thyme, rubbed            | 275877       | 1              |
| Bombastus       | Thyme, rubbed            | 280782       | 1              |
| Bombastus       | Thyme, rubbed            | 277466       | 1              |
| Bombastus       | Thyme, rubbed            | 267394       | 1              |
| Bombastus       | Thyme, rubbed            | 277996       | 3              |
| Bombastus       | Thyme, rubbed            | 268912       | 1              |
| Bombastus       | Turmeric, javanese, cut  | 284242       | 2              |
| Bombastus       | Turmeric, javanese, cut  | 262792       | 1              |
| Bombastus       | Turmeric, javanese, cut  | 282221       | 2              |
| Bombastus       | Valerian root, cut       | 268458       | 3              |
| Bombastus       | Valerian root, cut       | 267863       | 1              |
| Bombastus       | Valerian root, cut       | 268057       | 1              |
| Bombastus       | Valerian root, cut       | 274722       | 1              |
| Bombastus       | Valerian root, cut       | 274561       | 1              |
| Bombastus       | Valerian root, cut       | 276645       | 2              |
| Bombastus       | Valerian root, cut       | 269457       | 1              |
| Bombastus       | Valerian root, cut       | 6641B110317  | 3              |
| Bombastus       | Walnut bark, cut         | 711B1206130  | 1              |
| Bombastus       | Walnut leaf, cut         | 267575       | 1              |
| Bombastus       | Wild pansy, cut          | 279314       | 3              |
| Bombastus       | Wild pansy, cut          | 270869       | 2              |
| Bombastus       | Wild pansy, cut          | 278106       | 1              |
| Bombastus       | Wild pansy, cut          | 276259       | 4              |
| Bombastus       | Wild pansy, cut          | 274237       | 2              |
| Bombastus       | Wild pansy, cut          | 272832       | 2              |

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| Supplier  | Substance                | Batch               | Spectra |
|-----------|--------------------------|---------------------|---------|
| Bombastus | Wild pansy, cut          | 27132               | 1       |
| Bombastus | Wild pansy, cut          | 282661              | 1       |
| Bombastus | Wild pansy, cut          | 220232              | 1       |
| Bombastus | Wild pansy, cut          | 280890              | 1       |
| Bombastus | Willow bark, cut         | 277005              | 4       |
| Bombastus | Willow bark, cut         | 275052              | 1       |
| Bombastus | Willow bark, cut         | 261615              | 1       |
| Bombastus | Willow bark, cut         | 270886              | 2       |
| Bombastus | Willow bark, cut         | 277847              | 1       |
| Bombastus | Willow bark, cut         | 282270              | 3       |
| Bombastus | Willow bark, cut         | 278458              | 3       |
| Bombastus | Willow bark, cut         | 288869              | 1       |
| Bombastus | Willow bark, cut         | 267927              | 1       |
| Bombastus | Willow bark, cut         | 281533              | 2       |
| Bombastus | Willow bark, cut         | 292710              | 1       |
| Bombastus | Willow bark, cut         | 161594              | 1       |
| Bombastus | Willow bark, cut         | 251385              | 1       |
| Bombastus | Willow bark, cut         | 265845              | 1       |
| Bombastus | Willowherb, small flo... | 259546              | 2       |
| Bombastus | Willowherb, small flo... | 268836              | 3       |
| Bombastus | Willowherb, small flo... | 281846              | 2       |
| Bombastus | Willowherb, small flo... | 278235              | 1       |
| Bombastus | Wormwood herb, cut       | 221868              | 1       |
| Bombastus | Wormwood herb, cut       | 281000              | 1       |
| Bombastus | Wormwood herb, cut       | 265417              | 3       |
| Bombastus | Yarrow herb, cut         | 276498              | 4       |
| Bombastus | Yarrow herb, cut         | 279023              | 3       |
| Bombastus | Yarrow herb, cut         | 273273              | 2       |
| Bombastus | Yarrow herb, cut         | 274284              | 3       |
| Bombastus | Yarrow herb, cut         | 274610              | 2       |
| Bombastus | Yarrow herb, cut         | 15006702            | 2       |
| Bombastus | Yarrow herb, cut         | 278315              | 5       |
| Bombastus | Yarrow herb, cut         | 277430              | 2       |
| Bombastus | Yarrow herb, cut         | 275964              | 1       |
| Bombastus | Yarrow herb, cut         | 268179              | 2       |
| Caaelo    | Sodium sulfate decahy... | 11294603            | 2       |
| Cae       | Bean shells, cut         | Int.Ch.313011       | 1       |
| Cae       | Bilberry fruit, dried    | 212172              | 1       |
| Cae       | Bitter fennel            | Int.Ch.314090       | 1       |
| Caelo     | Abrotani herb, cut       | 2091305             | 1       |
| Caelo     | Acorus root, natural,... | 12066501            | 1       |
| Caelo     | Acorus root, natural,... | 13127801            | 1       |
| Caelo     | Acorus root, natural,... | 284875              | 2       |
| Caelo     | Acorus root, peeled      | 7061302             | 1       |
| Caelo     | Acorus root, peeled      | 12056701            | 2       |
| Caelo     | Acorus root, peeled      | 12066502            | 2       |
| Caelo     | Acorus root, peeled      | 12275602            | 7       |
| Caelo     | Acorus root, peeled      | 12066501            | 8       |
| Caelo     | Acorus root, peeled      | 12275604-3544411013 | 1       |
| Caelo     | Acorus root, peeled      | 12239008            | 1       |
| Caelo     | Acorus root, peeled      | 12295901            | 3       |
| Caelo     | Acorus root, peeled      | 12295902            | 4       |
| Caelo     | Acorus root, peeled      | 12056704            | 1       |
| Caelo     | Acorus root, peeled      | 12275604            | 2       |
| Caelo     | Acorus root, peeled      | 12056703            | 2       |
| Caelo     | Acorus root, peeled      | 12295903            | 1       |
| Caelo     | Acorus root, peeled      | 28121205            | 1       |
| Caelo     | Acorus root, peeled      | 12295904            | 4       |
| Caelo     | Acorus root, peeled      | 15061202            | 1       |
| Caelo     | Acorus root, peeled      | 12056702            | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>  | <b>Spectra</b> |
|-----------------|--------------------------|---------------|----------------|
| Caelo           | Acorus root, peeled      | 11054205      | 1              |
| Caelo           | Acorus root, peeled      | 11054204      | 1              |
| Caelo           | Acorus root, peeled      | 313060        | 1              |
| Caelo           | Acorus root, peeled      | 2913M-02173   | 1              |
| Caelo           | Acorus root, peeled      | 8031306       | 1              |
| Caelo           | Acorus root, peeled      | 13101306      | 1              |
| Caelo           | Acorus root, peeled      | 241013010     | 1              |
| Caelo           | Acorus root, peeled      | 24081203      | 1              |
| Caelo           | Acorus root, peeled      | 2211a-02173   | 1              |
| Caelo           | Acorus root, peeled      | 18011301      | 1              |
| Caelo           | Agarikon                 | 11024502      | 1              |
| Caelo           | Agnus castus fruit       | 12016909      | 4              |
| Caelo           | Agnus castus fruit       | 12016907      | 1              |
| Caelo           | Agnus castus fruit       | 3413A-03015   | 1              |
| Caelo           | Agnus castus fruit       | 12016904      | 1              |
| Caelo           | Agnus castus fruit       | 11026318      | 1              |
| Caelo           | Agnus castus fruit       | 13193410      | 2              |
| Caelo           | Agnus castus fruit       | 11026309      | 1              |
| Caelo           | Agnus castus fruit       | 1513546       | 1              |
| Caelo           | Agnus castus fruit       | 15318718      | 1              |
| Caelo           | Agnus castus fruit       | 15318702      | 1              |
| Caelo           | Agnus castus fruit       | 80175158      | 2              |
| Caelo           | Agnus castus fruit       | 15065105      | 1              |
| Caelo           | Agnus castus fruit       | 14194408      | 1              |
| Caelo           | Agnus castus fruit       | nachprüfung   | 1              |
| Caelo           | Agnus castus fruit       | 12274002      | 1              |
| Caelo           | Agnus castus fruit       | 12274001      | 1              |
| Caelo           | Agnus castus fruit       | 12274012      | 1              |
| Caelo           | Agnus castus fruit       | 13193406      | 3              |
| Caelo           | Agnus castus fruit       | 15065102      | 2              |
| Caelo           | Agnus castus fruit       | 13193404      | 1              |
| Caelo           | Agnus castus fruit       | 13193401      | 2              |
| Caelo           | Agnus castus fruit       | 12016903      | 1              |
| Caelo           | Agnus castus fruit       | 12016908      | 1              |
| Caelo           | Agnus castus fruit       | 12274009      | 2              |
| Caelo           | Agnus castus fruit       | 12274010      | 10             |
| Caelo           | Agnus castus fruit       | 12274003      | 7              |
| Caelo           | Agnus castus fruit       | 12274013      | 2              |
| Caelo           | Agnus castus fruit       | 13193403      | 1              |
| Caelo           | Agnus castus fruit       | 12274014      | 1              |
| Caelo           | Agnus castus fruit       | 12016905      | 2              |
| Caelo           | Agrimony, cut            | 10325502      | 2              |
| Caelo           | Agrimony, cut            | 10325505      | 2              |
| Caelo           | Agrimony, cut            | 3481-A-110324 | 1              |
| Caelo           | Agrimony, cut            | 10325501      | 1              |
| Caelo           | Agrimony, cut            | 9300110       | 1              |
| Caelo           | Agrimony, cut            | 10325504      | 1              |
| Caelo           | Agrimony, cut            | 11374005      | 2              |
| Caelo           | Agrimony, cut            | 1137407       | 1              |
| Caelo           | Agrimony, cut            | 10325503      | 5              |
| Caelo           | Agrimony, cut            | 12382901      | 3              |
| Caelo           | Agrimony, cut            | 11374002      | 4              |
| Caelo           | Agrimony, cut            | 11374006      | 8              |
| Caelo           | Agrimony, cut            | 12382905      | 6              |
| Caelo           | Agrimony, cut            | 12382903      | 1              |
| Caelo           | Agrimony, cut            | 21081205      | 1              |
| Caelo           | Agrimony, cut            | 9300107       | 1              |
| Caelo           | Agrimony, cut            | 11374004      | 8              |
| Caelo           | Alchemilla alpina her... | 12147205      | 2              |
| Caelo           | Alchemilla alpina her... | 12147203      | 1              |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Alchemilla alpina her... | 12147206            | 3       |
| Caelo    | Alchemilla alpina her... | 12147202            | 3       |
| Caelo    | Alchemilla alpina her... | 1214204             | 1       |
| Caelo    | Alchemilla alpina her... | 11063608            | 1       |
| Caelo    | Alchemilla alpina her... | 12147203-3470312131 | 1       |
| Caelo    | Alchemilla, cut          | 2101211616          | 1       |
| Caelo    | Alchemilla, cut          | 13141101            | 8       |
| Caelo    | Alchemilla, cut          | 13141105            | 3       |
| Caelo    | Alchemilla, cut          | 13141106            | 11      |
| Caelo    | Alchemilla, cut          | 11063605            | 1       |
| Caelo    | Alchemilla, cut          | 9011405             | 1       |
| Caelo    | Alchemilla, cut          | 1213309             | 1       |
| Caelo    | Alchemilla, cut          | 1406211616          | 1       |
| Caelo    | Alchemilla, cut          | 14066002            | 2       |
| Caelo    | Alchemilla, cut          | 13141103-3382319003 | 1       |
| Caelo    | Alchemilla, cut          | 14066003            | 2       |
| Caelo    | Alchemilla, cut          | 14066008            | 1       |
| Caelo    | Alchemilla, cut          | 15147002            | 2       |
| Caelo    | Alchemilla, cut          | 5041301             | 1       |
| Caelo    | Alchemilla, cut          | 2081304             | 1       |
| Caelo    | Alchemilla, cut          | 21081203            | 1       |
| Caelo    | Alchemilla, cut          | 27011401            | 1       |
| Caelo    | Alchemilla, cut          | 29131-01616         | 1       |
| Caelo    | Alchemilla, cut          | 8121201             | 1       |
| Caelo    | Alchemilla, cut          | 13141103            | 41      |
| Caelo    | Alchemilla, cut          | 13141102            | 7       |
| Caelo    | Alchemilla, cut          | 13141103-3400310161 | 1       |
| Caelo    | Alchemilla, cut          | 1182806             | 1       |
| Caelo    | Alchemilla, cut          | 11182808            | 1       |
| Caelo    | Alchemilla, cut          | 11182807            | 4       |
| Caelo    | Alchemilla, cut          | 1215305             | 2       |
| Caelo    | Alchemilla, cut          | 1215309             | 1       |
| Caelo    | Alchemilla, cut          | 12153303            | 8       |
| Caelo    | Alchemilla, cut          | 12153305            | 30      |
| Caelo    | Alchemilla, cut          | 11182805            | 4       |
| Caelo    | Alchemilla, cut          | 12153306            | 10      |
| Caelo    | Alchemilla, cut          | 12153307            | 3       |
| Caelo    | Alchemilla, cut          | 12342901            | 1       |
| Caelo    | Alchemilla, cut          | 1118206             | 1       |
| Caelo    | Alchemilla, cut          | 13141106-3545412081 | 1       |
| Caelo    | Alchemilla, cut          | 125306              | 1       |
| Caelo    | Alchemilla, cut          | 13091304            | 1       |
| Caelo    | Alchemilla, cut          | 131411002           | 1       |
| Caelo    | Alchemilla, cut          | 13141103-3456311103 | 1       |
| Caelo    | Alchemilla, cut          | 3613M01616          | 1       |
| Caelo    | Alchemilla, cut          | 5013I1616           | 1       |
| Caelo    | Alchemilla, cut          | 13141110            | 1       |
| Caelo    | Alchemilla, cut          | H-040513-2          | 1       |
| Caelo    | Alchemilla, cut          | 11182804            | 5       |
| Caelo    | Alchemilla, cut          | 11182803            | 1       |
| Caelo    | Alchemilla, cut          | 11182801            | 5       |
| Caelo    | Alchemilla, cut          | 1100912             | 1       |
| Caelo    | Alchemilla, cut          | 11002906            | 7       |
| Caelo    | Alchemilla, cut          | 12153301            | 5       |
| Caelo    | Alchemilla, cut          | 12153302            | 19      |
| Caelo    | Alchemilla, cut          | 11002907            | 4       |
| Caelo    | Alchemilla, cut          | 9346207             | 1       |
| Caelo    | Alchemilla, cut          | 1182808             | 1       |
| Caelo    | Alchemilla, cut          | intch:318080        | 1       |
| Caelo    | Almonds, bitter, whole   | 12239604            | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b> | <b>Spectra</b> |
|-----------------|--------------------------|--------------|----------------|
| Caelo           | Almonds, bitter, whole   | 16221202     | 1              |
| Caelo           | Almonds, bitter, whole   | 15193103     | 1              |
| Caelo           | Almonds, bitter, whole   | 5121301      | 1              |
| Caelo           | Almonds, bitter, whole   | 13242001     | 1              |
| Caelo           | Aloes, cape, cut         | 12338201     | 4              |
| Caelo           | Aloes, cape, cut         | 16202401     | 1              |
| Caelo           | Aloes, cape, cut         | 25071402     | 1              |
| Caelo           | Aloes, cape, cut         | 1313M-01089  | 1              |
| Caelo           | Aloes, cape, cut         | 12338203     | 4              |
| Caelo           | Aloes, cape, cut         | 25111303     | 1              |
| Caelo           | Aloes, cape, cut         | 12232102     | 3              |
| Caelo           | Aloes, cape, cut         | 12338206     | 3              |
| Caelo           | Aloes, cape, cut         | 15283001     | 1              |
| Caelo           | Aloes, cape, cut         | 11041402     | 1              |
| Caelo           | Aloes, cape, cut         | 12338209     | 2              |
| Caelo           | Aloes, cape, cut         | 11061406     | 1              |
| Caelo           | Aloes, cape, cut         | 11048808     | 1              |
| Caelo           | Aloes, cape, cut         | 12232105     | 1              |
| Caelo           | Aloes, cape, cut         | 505125       | 1              |
| Caelo           | Aloes, cape, powdered    | 12183013     | 3              |
| Caelo           | Aloes, cape, powdered    | 11132116     | 2              |
| Caelo           | Aloes, cape, powdered    | 11132115     | 1              |
| Caelo           | Aloes, cape, powdered    | 15125403     | 1              |
| Caelo           | Aloes, cape, powdered    | 14065905     | 1              |
| Caelo           | Aloes, cape, powdered    | 15206507     | 1              |
| Caelo           | Aloes, cape, powdered    | 11132116     | 1              |
| Caelo           | Aloes, cape, powdered    | 12183001     | 2              |
| Caelo           | Aloes, cape, powdered    | 14065906     | 1              |
| Caelo           | Aloes, cape, powdered    | 12183007     | 1              |
| Caelo           | Aloes, cape, powdered    | 12183005     | 2              |
| Caelo           | Aloes, cape, powdered    | 12183009     | 3              |
| Caelo           | Aloes, cape, powdered    | 12183008     | 1              |
| Caelo           | Aluminium chloride he... | 23071204     | 1              |
| Caelo           | Aluminium chloride he... | 18061308     | 1              |
| Caelo           | Aluminium chloride he... | 15080715     | 1              |
| Caelo           | Aluminium chloride he... | 10251307     | 1              |
| Caelo           | Aluminium chloride he... | 15080701     | 1              |
| Caelo           | Aluminium chloride he... | 8031301      | 1              |
| Caelo           | Aluminium chloride he... | 51/AD1       | 1              |
| Caelo           | Aluminium chloride he... | 3113E-01095  | 1              |
| Caelo           | Aluminium chloride he... | 12323710     | 8              |
| Caelo           | Aluminium chloride he... | 28121301     | 1              |
| Caelo           | Aluminium chloride he... | 27081301     | 1              |
| Caelo           | Aluminium chloride he... | 9071303      | 1              |
| Caelo           | Aluminium chloride he... | 12114906     | 7              |
| Caelo           | Aluminium chloride he... | 12114910     | 9              |
| Caelo           | Aluminium chloride he... | 12323703     | 1              |
| Caelo           | Aluminium chloride he... | 23051205     | 1              |
| Caelo           | Aluminium chloride he... | 12114907     | 1              |
| Caelo           | Aluminium chloride he... | 1210014-01   | 23             |
| Caelo           | Aluminium chloride he... | 13G03-N02    | 25             |
| Caelo           | Aluminium chloride he... | 121149006    | 1              |
| Caelo           | Aluminium chloride he... | 10251309     | 1              |
| Caelo           | Aluminium chloride he... | 10251314     | 1              |
| Caelo           | Aluminium chloride he... | 12114904     | 2              |
| Caelo           | Aluminium chloride he... | 121001402    | 2              |
| Caelo           | Aluminium chloride he... | 2313A-01095  | 1              |
| Caelo           | Aluminium chloride he... | 12114908     | 13             |
| Caelo           | Aluminium chloride he... | 23111203     | 1              |
| Caelo           | Aluminium chloride he... | 19041302     | 1              |

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| Supplier | Substance                | Batch            | Spectra |
|----------|--------------------------|------------------|---------|
| Caelo    | Aluminium chloride he... | 5081301          | 1       |
| Caelo    | Aluminium chloride he... | 1406021-01       | 3       |
| Caelo    | Aluminium chloride he... | 12021303         | 1       |
| Caelo    | Aluminium chloride he... | 12127-N01        | 1       |
| Caelo    | Aluminium chloride he... | 12323717         | 5       |
| Caelo    | Aluminium chloride he... | 130701101        | 1       |
| Caelo    | Aluminium chloride he... | 12114919         | 1       |
| Caelo    | Aluminium chloride he... | 1233702          | 1       |
| Caelo    | Aluminium chloride he... | 13L13-B03-287298 | 1       |
| Caelo    | Aluminium chloride he... | 12114922         | 19      |
| Caelo    | Aluminium chloride he... | 3091205          | 1       |
| Caelo    | Aluminium chloride he... | 15051302         | 1       |
| Caelo    | Aluminium chloride he... | 11229905         | 1       |
| Caelo    | Aluminium chloride he... | 11229906         | 1       |
| Caelo    | Aluminium chloride he... | 11229907         | 1       |
| Caelo    | Aluminium chloride he... | 12114920         | 13      |
| Caelo    | Aluminium chloride he... | 11229914         | 2       |
| Caelo    | Aluminium chloride he... | 11229917         | 4       |
| Caelo    | Aluminium chloride he... | 13/13-B03-287298 | 1       |
| Caelo    | Aluminium chloride he... | 12323711         | 21      |
| Caelo    | Aluminium chloride he... | 12047514         | 5       |
| Caelo    | Aluminium chloride he... | 12114912         | 7       |
| Caelo    | Aluminium chloride he... | 12114918         | 18      |
| Caelo    | Aluminium chloride he... | 12047503         | 3       |
| Caelo    | Aluminium chloride he... | 11229913         | 2       |
| Caelo    | Aluminium chloride he... | 12047505         | 4       |
| Caelo    | Aluminium potassium s... | 12022409         | 1       |
| Caelo    | Aluminium potassium s... | 13025401         | 4       |
| Caelo    | Aluminium potassium s... | 12144603         | 1       |
| Caelo    | Aluminium potassium s... | 15172501         | 1       |
| Caelo    | Aluminium potassium s... | 12022406         | 3       |
| Caelo    | Aluminium potassium s... | 14263804         | 1       |
| Caelo    | Aluminium potassium s... | 13025404         | 2       |
| Caelo    | Aluminium potassium s... | 13356103         | 2       |
| Caelo    | Aluminium potassium s... | 11G01-N04        | 1       |
| Caelo    | Aluminium potassium s... | 12022404         | 3       |
| Caelo    | Aluminium potassium s... | 12022406         | 2       |
| Caelo    | Aluminium potassium s... | 12184401         | 1       |
| Caelo    | Aluminium potassium s... | 90033229         | 1       |
| Caelo    | Aluminium potassium s... | 11254805         | 1       |
| Caelo    | Aluminium potassium s... | 11218611         | 3       |
| Caelo    | Aluminium potassium s... | 12 24-M03        | 1       |
| Caelo    | Aluminium potassium s... | 12239102         | 2       |
| Caelo    | Aluminium potassium s... | 13098702         | 1       |
| Caelo    | Aluminium potassium s... | 12184408         | 3       |
| Caelo    | Aluminium potassium s... | 12184407         | 3       |
| Caelo    | Aluminium potassium s... | 12184407         | 6       |
| Caelo    | Aluminium potassium s... | 12022444         | 1       |
| Caelo    | Aluminium potassium s... | 11017211         | 1       |
| Caelo    | Aluminium potassium s... | 12144605         | 4       |
| Caelo    | Aluminium potassium s... | 12144607         | 2       |
| Caelo    | Aluminium potassium s... | 510211092        | 1       |
| Caelo    | Aluminium potassium s... | 2713Q1092        | 1       |
| Caelo    | Aluminium potassium s... | 504311092        | 1       |
| Caelo    | Aluminium potassium s... | 1218411          | 1       |
| Caelo    | Aluminium potassium s... | 12144602         | 1       |
| Caelo    | Aluminium potassium s... | 12184401         | 3       |
| Caelo    | Aluminium potassium s... | 13025414         | 1       |
| Caelo    | Aluminium potassium s... | 12184411         | 5       |
| Caelo    | Aluminium potassium s... | 12022404         | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>  | <b>Spectra</b> |
|-----------------|--------------------------|---------------|----------------|
| Caelo           | Ammonium chloride        | 12356101      | 3              |
| Caelo           | Ammonium chloride        | 12240302      | 4              |
| Caelo           | Ammonium chloride        | 10176319      | 3              |
| Caelo           | Ammonium chloride        | 10176309      | 1              |
| Caelo           | Ammonium hydrogen car... | 13104601      | 1              |
| Caelo           | Ammonium hydrogen car... | 3091204       | 1              |
| Caelo           | Ammonium hydrogen car... | 72715338      | 2              |
| Caelo           | Ammonium hydrogen car... | 4112M-01103   | 1              |
| Caelo           | Ammonium hydrogen car... | 12322204      | 1              |
| Caelo           | Ammonium hydrogen car... | 25111308      | 1              |
| Caelo           | Ammonium hydrogen car... | 24101202      | 1              |
| Caelo           | Ammonium hydrogen car... | 3712Q-01103   | 1              |
| Caelo           | Ammonium hydrogen car... | 9139402       | 1              |
| Caelo           | Ammonium hydrogen car... | 23101204      | 1              |
| Caelo           | Ammonium hydrogen car... | 11145612      | 3              |
| Caelo           | Ammonium hydrogen car... | 12322201      | 1              |
| Caelo           | Ammonium hydrogen car... | 23011404      | 1              |
| Caelo           | Ammonium hydrogen car... | 13104611      | 1              |
| Caelo           | Amphetamine sulfate      | 13344605      | 1              |
| Caelo           | Amphetamine sulfate      | 12B06-N013    | 1              |
| Caelo           | Amphetamine sulfate      | 12095607      | 1              |
| Caelo           | Amphetamine sulfate      | 15193204      | 1              |
| Caelo           | Amphetamine sulfate      | 15L01-B05     | 2              |
| Caelo           | Amphetamine sulfate      | lot067002     | 1              |
| Caelo           | Amphetamine sulfate      | 12I24-N03     | 1              |
| Caelo           | Amphetamine sulfate      | 13344602      | 1              |
| Caelo           | Amphetamine sulfate      | 16153909      | 1              |
| Caelo           | Angelica root            | 12350703      | 9              |
| Caelo           | Angelica root            | 15162604      | 2              |
| Caelo           | Angelica root            | 11259803      | 1              |
| Caelo           | Angelica root            | Int.Ch:318090 | 1              |
| Caelo           | Angelica root            | 16128002      | 1              |
| Caelo           | Angelica root            | 28101402      | 1              |
| Caelo           | Angelica root            | 303299        | 1              |
| Caelo           | Angelica root            | 5162606       | 1              |
| Caelo           | Angelica root            | 14179506      | 2              |
| Caelo           | Angelica root            | 11093304      | 1              |
| Caelo           | Angelica root            | 12070806      | 1              |
| Caelo           | Angelica root            | 12345         | 1              |
| Caelo           | Angelica root            | 269775        | 3              |
| Caelo           | Angelica root            | 12080403      | 1              |
| Caelo           | Angelica root            | 12080412      | 1              |
| Caelo           | Angelica root            | 5091303       | 1              |
| Caelo           | Angelica root            | 9030301       | 1              |
| Caelo           | Angelica root            | 11093310      | 1              |
| Caelo           | Angelica root            | 12350704      | 2              |
| Caelo           | Angelica root            | 10071306      | 1              |
| Caelo           | Angelica root            | 12168701      | 5              |
| Caelo           | Angelica root            | 12350705      | 1              |
| Caelo           | Angelica root            | 12168705      | 2              |
| Caelo           | Angelica root            | 15101304      | 1              |
| Caelo           | Angelica root            | 21011402      | 1              |
| Caelo           | Angelica root            | 274128        | 4              |
| Caelo           | Angelica root            | 14178506      | 1              |
| Caelo           | Angelica root            | 12350701      | 1              |
| Caelo           | Angelica root            | 3412Q-02127   | 1              |
| Caelo           | Angelica root            | 12168702      | 2              |
| Caelo           | Angelica root            | 30011302      | 1              |
| Caelo           | Aniseed                  | 3314E-01530   | 1              |
| Caelo           | Aniseed                  | 15398605      | 3              |

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| Supplier | Substance        | Batch               | Spectra |
|----------|------------------|---------------------|---------|
| Caelo    | Aniseed          | 21021312            | 1       |
| Caelo    | Aniseed          | 16165303            | 1       |
| Caelo    | Aniseed          | 15398603            | 2       |
| Caelo    | Aniseed          | 2215M-01530         | 1       |
| Caelo    | Aniseed          | 16165304            | 1       |
| Caelo    | Aniseed          | 16165305            | 2       |
| Caelo    | Aniseed          | 16165306            | 1       |
| Caelo    | Aniseed          | 2213M-01530         | 1       |
| Caelo    | Aniseed          | 17045603            | 1       |
| Caelo    | Aniseed          | 411081/1            | 1       |
| Caelo    | Aniseed          | 2916E-01530         | 1       |
| Caelo    | Aniseed          | 2700A140129         | 7       |
| Caelo    | Aniseed          | 13037809            | 14      |
| Caelo    | Aniseed          | 11370304            | 10      |
| Caelo    | Aniseed          | 11370308            | 6       |
| Caelo    | Aniseed          | 1137033             | 1       |
| Caelo    | Aniseed          | 12360801            | 1       |
| Caelo    | Aniseed          | 13037802            | 11      |
| Caelo    | Aniseed          | 13037803            | 2       |
| Caelo    | Aniseed          | 11370303            | 15      |
| Caelo    | Aniseed          | 13037804            | 8       |
| Caelo    | Aniseed          | 13037806            | 2       |
| Caelo    | Aniseed          | 13037807            | 1       |
| Caelo    | Aniseed          | 13037808            | 12      |
| Caelo    | Aniseed          | 1307809             | 1       |
| Caelo    | Aniseed          | 133333902           | 1       |
| Caelo    | Aniseed          | 13333901            | 6       |
| Caelo    | Aniseed          | 13037805            | 13      |
| Caelo    | Aniseed          | 13333903            | 6       |
| Caelo    | Aniseed          | 11370302            | 7       |
| Caelo    | Aniseed          | 111101213           | 1       |
| Caelo    | Aniseed          | 2700A130527         | 15      |
| Caelo    | Aniseed          | 4061301             | 1       |
| Caelo    | Aniseed          | 5061301             | 1       |
| Caelo    | Aniseed          | 5091304             | 1       |
| Caelo    | Aniseed          | 5121401             | 1       |
| Caelo    | Aniseed          |                     | 1       |
| Caelo    | Aniseed          | 11370301            | 11      |
| Caelo    | Aniseed          | 10081207            | 1       |
| Caelo    | Aniseed          | 10247203            | 3       |
| Caelo    | Aniseed          | 11101202            | 3       |
| Caelo    | Aniseed          | 11101204            | 1       |
| Caelo    | Aniseed          | 11101213            | 7       |
| Caelo    | Aniseed          | 11101214            | 7       |
| Caelo    | Aniseed          | 11101215            | 3       |
| Caelo    | Aniseed          | 10247202            | 1       |
| Caelo    | Aniseed          | 13333906            | 3       |
| Caelo    | Aniseed          | 13037901            | 1       |
| Caelo    | Aniseed          | 13333910            | 4       |
| Caelo    | Aniseed          | 13037808-3560412014 | 1       |
| Caelo    | Aniseed          | 140913a             | 1       |
| Caelo    | Aniseed          | 15046101            | 8       |
| Caelo    | Aniseed          | 15046102            | 6       |
| Caelo    | Aniseed          | 15046107            | 1       |
| Caelo    | Aniseed          | 15046109            | 4       |
| Caelo    | Aniseed          | 13333914            | 1       |
| Caelo    | Aniseed          | 15283201            | 3       |
| Caelo    | Aniseed          | 13333908            | 12      |
| Caelo    | Aniseed          | 13333909            | 2       |
| Caelo    | Aniseed, pounded | 11242003            | 1       |

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| <b>Supplier</b> | <b>Substance</b>        | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|-------------------------|---------------------|----------------|
| Caelo           | Aniseed, pounded        | 13149902            | 1              |
| Caelo           | Aniseed, pounded        | 12111301            | 1              |
| Caelo           | Aniseed, pounded        | 12111303            | 3              |
| Caelo           | Aniseed, pounded        | 12111304            | 1              |
| Caelo           | Aniseed, pounded        | 12360803            | 2              |
| Caelo           | Aniseed, pounded        | 4041302             | 1              |
| Caelo           | Aniseed, pounded        | 23041303            | 1              |
| Caelo           | Aniseed, pounded        | 15149702            | 1              |
| Caelo           | Apple, cut              | 12227301            | 1              |
| Caelo           | Arnica flower           | 12227203            | 1              |
| Caelo           | Arnica flower           | 10207405            | 2              |
| Caelo           | Arnica flower           | 6112013A            | 1              |
| Caelo           | Arnica flower           | 10081204            | 1              |
| Caelo           | Arnica flower           | 11259803            | 2              |
| Caelo           | Arnica flower           | 11374105            | 1              |
| Caelo           | Arnica flower           | 11259804            | 1              |
| Caelo           | Arnica flower           | 11285703            | 1              |
| Caelo           | Arnica flower           | 11374102            | 3              |
| Caelo           | Arnica flower           | 11374103            | 1              |
| Caelo           | Arnica flower           | 11374101            | 2              |
| Caelo           | Arnica flower           | 12227202            | 1              |
| Caelo           | Arnica flower           | IntCh: 212032       | 1              |
| Caelo           | Arnica flower           | 28071201            | 1              |
| Caelo           | Arnica flower           | 1222702             | 1              |
| Caelo           | Arnica flower           | 122227202           | 1              |
| Caelo           | Arnica flower           | 11285705            | 1              |
| Caelo           | Artichoke leaf, cut     | 11151908            | 2              |
| Caelo           | Artichoke leaf, cut     | 81232298            | 1              |
| Caelo           | Artichoke leaf, cut     | 13310706            | 1              |
| Caelo           | Artichoke leaf, cut     | 12173307-3260315072 | 1              |
| Caelo           | Artichoke leaf, cut     | 3110Q-03593         | 1              |
| Caelo           | Artichoke leaf, cut     | 2312I-03593         | 1              |
| Caelo           | Artichoke leaf, cut     | 13037607            | 4              |
| Caelo           | Artichoke leaf, cut     | 13037605            | 1              |
| Caelo           | Artichoke leaf, cut     | 13037603            | 3              |
| Caelo           | Artichoke leaf, cut     | 12173307            | 6              |
| Caelo           | Artichoke leaf, cut     | 12173306            | 2              |
| Caelo           | Artichoke leaf, cut     | 12173304            | 2              |
| Caelo           | Artichoke leaf, cut     | 12173302            | 3              |
| Caelo           | Artichoke leaf, cut     | 13037608            | 1              |
| Caelo           | Artichoke leaf, cut     | nachprüfung         | 2              |
| Caelo           | Ash leaf, cut           | 9344908             | 1              |
| Caelo           | Ash leaf, cut           | 12225502            | 1              |
| Caelo           | Ash leaf, cut           | 12225504            | 1              |
| Caelo           | Ash leaf, cut           | 12225505            | 2              |
| Caelo           | Asparagus root, cut     | 13071002            | 2              |
| Caelo           | Asparagus root, cut     | 13193302            | 1              |
| Caelo           | Barberries              | 12217107            | 1              |
| Caelo           | Barberries              | 12217106            | 1              |
| Caelo           | Barberries              | 12217103            | 3              |
| Caelo           | Barberries              | 11058320            | 1              |
| Caelo           | Barberries              | 1221707             | 1              |
| Caelo           | Barberries              | 12217116            | 1              |
| Caelo           | Barberries              | 12217111            | 1              |
| Caelo           | Barberries              | 12217113            | 2              |
| Caelo           | Barberry root bark, cut | 12112601            | 1              |
| Caelo           | Barberry root bark, cut | 11083507            | 1              |
| Caelo           | Barberry root bark, cut | 12112602            | 2              |
| Caelo           | Barberry root bark, cut | 12112603            | 2              |
| Caelo           | Barberry root bark, cut | 12112605            | 1              |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Barberry root bark, cut  | 12112606            | 4       |
| Caelo    | Barberry root bark, cut  | 12112608            | 1       |
| Caelo    | Barberry root bark, cut  | nachprüfung         | 1       |
| Caelo    | Barberry root bark, cut  | 11083509            | 1       |
| Caelo    | Barberry root bark, cut  | 55B110128           | 1       |
| Caelo    | Basil, rubbed            | 12066404            | 3       |
| Caelo    | Basil, rubbed            | 13048605-3519411022 | 1       |
| Caelo    | Basil, rubbed            | nachprüfung         | 1       |
| Caelo    | Basil, rubbed            | 3632A110201         | 4       |
| Caelo    | Basil, rubbed            | 13048601            | 2       |
| Caelo    | Basil, rubbed            | 12007008            | 2       |
| Caelo    | Basil, rubbed            | 12007010            | 4       |
| Caelo    | Basil, rubbed            | 13048605            | 2       |
| Caelo    | Bean shells, cut         | 15060905            | 1       |
| Caelo    | Bean shells, cut         | 13333803            | 1       |
| Caelo    | Bean shells, cut         | 14080002            | 1       |
| Caelo    | Bean shells, cut         | 29091201            | 1       |
| Caelo    | Bean shells, cut         | 1333802             | 1       |
| Caelo    | Bean shells, cut         | 12358703            | 4       |
| Caelo    | Bean shells, cut         | 11030601            | 1       |
| Caelo    | Bean shells, cut         | 13333801            | 1       |
| Caelo    | Bean shells, cut         | 11233603            | 2       |
| Caelo    | Bean shells, cut         | 11030604            | 6       |
| Caelo    | Bean shells, cut         | 1103061             | 1       |
| Caelo    | Bean shells, cut         | 6031301             | 1       |
| Caelo    | Bean shells, cut         | 11030605            | 1       |
| Caelo    | Bean shells, cut         | 10006507            | 1       |
| Caelo    | Bean shells, cut         | 10006504            | 1       |
| Caelo    | Bean shells, cut         | 8301004             | 1       |
| Caelo    | Bearberry leaf, cut      | 20111210            | 1       |
| Caelo    | Bearberry leaf, cut      | 280889              | 3       |
| Caelo    | Bearberry leaf, cut      | 2811Q-01518         | 1       |
| Caelo    | Bearberry leaf, cut      | 3108201204          | 1       |
| Caelo    | Bearberry leaf, cut      | 1218602             | 1       |
| Caelo    | Bearberry leaf, cut      | 11213003            | 1       |
| Caelo    | Bearberry leaf, cut      | 13067805-3390311080 | 1       |
| Caelo    | Bearberry leaf, cut      | 17121306            | 1       |
| Caelo    | Bearberry leaf, cut      | 15116201            | 1       |
| Caelo    | Bearberry leaf, cut      | 92795616            | 1       |
| Caelo    | Bearberry leaf, cut      | 13067805            | 7       |
| Caelo    | Bearberry leaf, cut      | 9279516             | 1       |
| Caelo    | Bearberry leaf, cut      | 15051303            | 1       |
| Caelo    | Bearberry leaf, cut      | 8120                | 1       |
| Caelo    | Bearberry leaf, cut      | 5111301             | 1       |
| Caelo    | Bearberry leaf, cut      | 4689145             | 1       |
| Caelo    | Bearberry leaf, cut      | 412A-01518          | 1       |
| Caelo    | Bearberry leaf, cut      | 4091301             | 1       |
| Caelo    | Bearberry leaf, cut      | 4021407             | 1       |
| Caelo    | Bearberry leaf, cut      | 11213005            | 5       |
| Caelo    | Bearberry leaf, cut      | 11213010            | 1       |
| Caelo    | Bearberry leaf, cut      | 9279515             | 1       |
| Caelo    | Bearberry leaf, cut      | 12186503            | 2       |
| Caelo    | Bearberry leaf, cut      | 12186504            | 1       |
| Caelo    | Bearberry leaf, cut      | 12186506            | 7       |
| Caelo    | Bearberry leaf, cut      | 12186502            | 2       |
| Caelo    | Bearberry leaf, cut      | 13067802            | 2       |
| Caelo    | Bentonite                | fürHerrSalloch      | 1       |
| Caelo    | Bentonite                | 1311014-01          | 1       |
| Caelo    | Bentonite                | 1307016-01          | 1       |
| Caelo    | Betamethasone-17-vale... | 12a05-no8           | 1       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Betamethasone-17-vale... | 12A05-N08           | 3       |
| Caelo    | Betony herb, cut         | 134048903           | 1       |
| Caelo    | Betony herb, cut         | 13367802            | 1       |
| Caelo    | Betony herb, cut         | 12007205            | 3       |
| Caelo    | Betony herb, cut         | 11247205            | 1       |
| Caelo    | Betony herb, cut         | 12007208            | 2       |
| Caelo    | Betony herb, cut         | 13048906            | 1       |
| Caelo    | Bilberry fruit, dried    | 18101307            | 1       |
| Caelo    | Bilberry fruit, dried    | 10273708            | 1       |
| Caelo    | Bilberry fruit, dried    | 10273709            | 1       |
| Caelo    | Bilberry fruit, dried    | 10273711            | 2       |
| Caelo    | Bilberry fruit, dried    | 12183701            | 2       |
| Caelo    | Bilberry fruit, dried    | 12183704            | 5       |
| Caelo    | Bilberry fruit, dried    | 10265601            | 1       |
| Caelo    | Bilberry fruit, dried    | 13130501            | 3       |
| Caelo    | Bilberry fruit, dried    | 13130504            | 1       |
| Caelo    | Bilberry fruit, dried    | 26061301            | 1       |
| Caelo    | Bilberry fruit, dried    | 10273707            | 1       |
| Caelo    | Bilberry fruit, dried    | 10265603            | 1       |
| Caelo    | Bilberry leaf, cut       | 1300907             | 1       |
| Caelo    | Bilberry leaf, cut       | 3091302             | 1       |
| Caelo    | Bilberry leaf, cut       | 9367603             | 2       |
| Caelo    | Bilberry leaf, cut       | 10222601            | 1       |
| Caelo    | Bilberry leaf, cut       | nachprüfung         | 1       |
| Caelo    | Bilberry leaf, cut       | 13009907            | 2       |
| Caelo    | Bilberry leaf, cut       | 23111201            | 1       |
| Caelo    | Bilberry leaf, cut       | 5110J-01506         | 1       |
| Caelo    | Bilberry leaf, cut       | 13009903            | 4       |
| Caelo    | Bilberry leaf, cut       | 13009901            | 3       |
| Caelo    | Bilberry leaf, cut       | 12140201            | 2       |
| Caelo    | Bilberry leaf, cut       | 12140204            | 5       |
| Caelo    | Bilberry leaf, cut       | 13009904            | 3       |
| Caelo    | Bilberry leaf, cut       | 12140206            | 2       |
| Caelo    | Bilberry leaf, cut       | 13009905            | 1       |
| Caelo    | Bilberry leaf, cut       | 12140205            | 1       |
| Caelo    | Birch leaf, cut          | 13108916            | 1       |
| Caelo    | Birch leaf, cut          | 12193108            | 1       |
| Caelo    | Birch leaf, cut          | 13108906            | 1       |
| Caelo    | Birch leaf, cut          | nachprüfung         | 1       |
| Caelo    | Birch leaf, cut          | 12193002            | 1       |
| Caelo    | Birch leaf, cut          | 13108905            | 9       |
| Caelo    | Birch leaf, cut          | 11189502            | 2       |
| Caelo    | Birch leaf, cut          | 11050102            | 4       |
| Caelo    | Birch leaf, cut          | 11189501            | 2       |
| Caelo    | Birch leaf, cut          | IntCh:311092        | 1       |
| Caelo    | Birch leaf, cut          | 13337303-3561412013 | 1       |
| Caelo    | Birch leaf, cut          | 261441              | 1       |
| Caelo    | Birch leaf, cut          | 3013E-01481         | 1       |
| Caelo    | Birch leaf, cut          | 14360703            | 1       |
| Caelo    | Birch leaf, cut          | 14360702            | 1       |
| Caelo    | Birch leaf, cut          | 13337303            | 1       |
| Caelo    | Birch leaf, cut          | 107063              | 1       |
| Caelo    | Birch leaf, cut          | 13337302            | 1       |
| Caelo    | Birch leaf, cut          | 11189507            | 1       |
| Caelo    | Birch leaf, cut          | 13108917            | 1       |
| Caelo    | Birch leaf, cut          | 11189509            | 1       |
| Caelo    | Birch leaf, cut          | 11189510            | 3       |
| Caelo    | Birch leaf, cut          | 12193003            | 1       |
| Caelo    | Birch leaf, cut          | 12193109            | 14      |
| Caelo    | Bitter fennel            | 15443202            | 2       |

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| Supplier | Substance     | Batch           | Spectra |
|----------|---------------|-----------------|---------|
| Caelo    | Bitter fennel | 12094725        | 8       |
| Caelo    | Bitter fennel | 12094703        | 2       |
| Caelo    | Bitter fennel | 11016330        | 1       |
| Caelo    | Bitter fennel | 6091201         | 1       |
| Caelo    | Bitter fennel | 5061302         | 1       |
| Caelo    | Bitter fennel | 4061302         | 1       |
| Caelo    | Bitter fennel | 402311545       | 1       |
| Caelo    | Bitter fennel | 1320041         | 1       |
| Caelo    | Bitter fennel | 13200401        | 4       |
| Caelo    | Bitter fennel | 1302081         | 1       |
| Caelo    | Bitter fennel | 13020802        | 7       |
| Caelo    | Bitter fennel | 13020801        | 4       |
| Caelo    | Bitter fennel | 12094704        | 8       |
| Caelo    | Bitter fennel | 9121305         | 1       |
| Caelo    | Bitter fennel | nachprüfung     | 1       |
| Caelo    | Bitter fennel | 12167102        | 3       |
| Caelo    | Bitter fennel | 1209474         | 1       |
| Caelo    | Bitter fennel | 12094711        | 1       |
| Caelo    | Bitter fennel | 12035102        | 2       |
| Caelo    | Bitter fennel | 2860A110704     | 6       |
| Caelo    | Bitter fennel | 16061202        | 1       |
| Caelo    | Bitter fennel | 11185501        | 1       |
| Caelo    | Bitter fennel | 1106330         | 1       |
| Caelo    | Bitter fennel | 11016332        | 1       |
| Caelo    | Bitter fennel | 11016331        | 5       |
| Caelo    | Bitter fennel | 7031306         | 1       |
| Caelo    | Bitter fennel | 12094710        | 6       |
| Caelo    | Bitter fennel | 12094712        | 6       |
| Caelo    | Bitter fennel | 12094715        | 6       |
| Caelo    | Bitter fennel | 27121201        | 1       |
| Caelo    | Bitter fennel | 15443203        | 2       |
| Caelo    | Bitter fennel | 15046107        | 1       |
| Caelo    | Bitter fennel | 15006501        | 3       |
| Caelo    | Bitter fennel | 14376408        | 1       |
| Caelo    | Bitter fennel | 14111301        | 1       |
| Caelo    | Bitter fennel | 13398505        | 1       |
| Caelo    | Bitter fennel | 13398502        | 3       |
| Caelo    | Bitter fennel | 13371610        | 1       |
| Caelo    | Bitter fennel | 13371605        | 1       |
| Caelo    | Bitter fennel | 13371604        | 1       |
| Caelo    | Bitter fennel | 13148307        | 3       |
| Caelo    | Bitter fennel | 13148306        | 1       |
| Caelo    | Bitter fennel | 13148305        | 4       |
| Caelo    | Bitter fennel | 13148304        | 23      |
| Caelo    | Bitter fennel | 13148303        | 2       |
| Caelo    | Bitter fennel | 12362710        | 1       |
| Caelo    | Bitter fennel | 12345678        | 1       |
| Caelo    | Bitter fennel | 12094726        | 1       |
| Caelo    | Bitter fennel | 12094724        | 4       |
| Caelo    | Bitter fennel | 12094721        | 4       |
| Caelo    | Bitter fennel | 12094720        | 7       |
| Caelo    | Bitter fennel | 12094719        | 5       |
| Caelo    | Bitter fennel | 12094717        | 1       |
| Caelo    | Bitter fennel | 12094716        | 10      |
| Caelo    | Bitter fennel | 11016309        | 1       |
| Caelo    | Bitter fennel | 10109010        | 1       |
| Caelo    | Bitter fennel | 12094710        | 1       |
| Caelo    | Bitter fennel | 154443204       | 1       |
| Caelo    | Bitter fennel | 14376408; 21S08 | 1       |
| Caelo    | Bitter fennel | 5121401         | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|--------------------------|---------------------|----------------|
| Caelo           | Bitter fennel            | 12094720            | 1              |
| Caelo           | Bitter fennel            | 13200402            | 2              |
| Caelo           | Bitter fennel            | 13371610            | 2              |
| Caelo           | Bitter fennel            | 13398502            | 1              |
| Caelo           | Bitter fennel            | 14255802            | 3              |
| Caelo           | Bitter fennel            | 14376401            | 1              |
| Caelo           | Bitter fennel            | 14376402            | 1              |
| Caelo           | Bitter fennel            | 11016318            | 1              |
| Caelo           | Bitter fennel            | 14376406            | 2              |
| Caelo           | Bitter fennel            | 14376408            | 6              |
| Caelo           | Bitter fennel            | 15006501            | 2              |
| Caelo           | Bitter fennel            | 15006506            | 1              |
| Caelo           | Bitter fennel            | 14376405            | 1              |
| Caelo           | Bitter fennel            | 15006508            | 2              |
| Caelo           | Bitter fennel            | 12167101            | 1              |
| Caelo           | Bitter fennel            | 15443215            | 1              |
| Caelo           | Bitter fennel            | 15443212            | 1              |
| Caelo           | Bitter fennel            | 15006507            | 2              |
| Caelo           | Bitter fennel            | 15443208            | 1              |
| Caelo           | Bitter fennel            | 4911E-1545          | 1              |
| Caelo           | Bitter fennel            | 15443209            | 2              |
| Caelo           | Bitter fennel            | 16298102            | 1              |
| Caelo           | Bitter fennel            | 15443204            | 4              |
| Caelo           | Bitter fennel            | 15443203            | 2              |
| Caelo           | Bitter fennel            | 12094716-3408310191 | 1              |
| Caelo           | Bitter fennel            | 15141004            | 1              |
| Caelo           | Bitter fennel            | 15007601            | 1              |
| Caelo           | Bitter fennel            | 13148304-3500411070 | 1              |
| Caelo           | Bitter orange flower ... | 12266705            | 2              |
| Caelo           | Bitter orange flower ... | 12266611            | 2              |
| Caelo           | Bitter orange flower ... | 12266605            | 1              |
| Caelo           | Bitter orange flower ... | 11049212            | 1              |
| Caelo           | Bitter orange flower ... | 2712E-01445         | 1              |
| Caelo           | Bitter orange flower ... | 13067903            | 3              |
| Caelo           | Bitter orange flower ... | 12266605            | 1              |
| Caelo           | Bitter orange flower ... | 12266608            | 2              |
| Caelo           | Bitter orange flower ... | 12266703            | 3              |
| Caelo           | Bitter orange flower ... | 12266708            | 1              |
| Caelo           | Bitter orange flower ... | 12266707            | 1              |
| Caelo           | Bitter orange flower ... | 12266608            | 7              |
| Caelo           | Bitter orange flower ... | 13352701-3518411022 | 1              |
| Caelo           | Bitter orange flower ... | 11049202            | 1              |
| Caelo           | Bitter orange flower ... | 6051301             | 1              |
| Caelo           | Bitter orange flower ... | 12266601            | 1              |
| Caelo           | Bitter orange flower ... | 12266609            | 1              |
| Caelo           | Bitter orange flower ... | 12266611            | 2              |
| Caelo           | Bitter orange flower ... | 13352701            | 1              |
| Caelo           | Bitter orange flower ... | 12266614            | 1              |
| Caelo           | Bitter orange peel, cut  | 4312M-01531         | 1              |
| Caelo           | Bitter orange peel, cut  | 21101302            | 1              |
| Caelo           | Bitter orange peel, cut  | 12067402            | 1              |
| Caelo           | Bitter orange peel, cut  | 12239203            | 4              |
| Caelo           | Bitter orange peel, cut  | 13049002            | 1              |
| Caelo           | Bitter orange peel, cut  | 13049001            | 1              |
| Caelo           | Bitter orange peel, cut  | 12067405            | 1              |
| Caelo           | Bitter orange peel, cut  | 17111201            | 1              |
| Caelo           | Bitter orange peel, cut  | 27011403            | 1              |
| Caelo           | Black cohosh, cut        | 10281118            | 2              |
| Caelo           | Black cohosh, cut        | 10281104            | 1              |
| Caelo           | Black cohosh, cut        | 13237901            | 2              |

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| Supplier | Substance                | Batch         | Spectra |
|----------|--------------------------|---------------|---------|
| Caelo    | Black cohosh, cut        | 13237903      | 1       |
| Caelo    | Black cohosh, cut        | 13142101      | 1       |
| Caelo    | Black cohosh, cut        | 10281112      | 1       |
| Caelo    | Black cohosh, cut        | 13237907      | 1       |
| Caelo    | Black cumin seed         | 12358901      | 4       |
| Caelo    | Black cumin seed         | 11233507      | 1       |
| Caelo    | Black cumin seed         | 10121916      | 1       |
| Caelo    | Black cumin seed         | 12358906      | 3       |
| Caelo    | Black cumin seed         | 11233503      | 2       |
| Caelo    | Black cumin seed         | 13326405      | 2       |
| Caelo    | Black cumin seed         | 12358904      | 1       |
| Caelo    | Black cumin seed         | 13122013b     | 1       |
| Caelo    | Black cumin seed         | 13326406      | 1       |
| Caelo    | Black cumin seed         | 14359903      | 3       |
| Caelo    | Black cumin seed         | 10121915      | 1       |
| Caelo    | Black cumin seed         | 12358903      | 2       |
| Caelo    | Black cumin seed         | 12358902      | 1       |
| Caelo    | Black cumin seed         | 11233502      | 2       |
| Caelo    | Black mustard seed       | 12189307      | 1       |
| Caelo    | Black mustard seed       | 14057702      | 1       |
| Caelo    | Black mustard seed       | 13038904      | 1       |
| Caelo    | Black mustard seed, p... | 12009706      | 2       |
| Caelo    | Black mustard seed, p... | 13097704      | 4       |
| Caelo    | Black mustard seed, p... | 16051807      | 1       |
| Caelo    | Black mustard seed, p... | 16051807      | 1       |
| Caelo    | Black mustard seed, p... | 16051810      | 1       |
| Caelo    | Black mustard seed, p... | 16272703      | 6       |
| Caelo    | Black mustard seed, p... | 14293713      | 1       |
| Caelo    | Black mustard seed, p... | 13358302      | 13      |
| Caelo    | Black mustard seed, p... | 16272704      | 1       |
| Caelo    | Black mustard seed, p... | 16333501      | 1       |
| Caelo    | Black mustard seed, p... | 2015Q-02244   | 1       |
| Caelo    | Black mustard seed, p... | 23061401      | 1       |
| Caelo    | Black mustard seed, p... | 12009702      | 5       |
| Caelo    | Black mustard seed, p... | 12350210      | 1       |
| Caelo    | Black mustard seed, p... | 1200970601-13 | 1       |
| Caelo    | Black mustard seed, p... | 16272707      | 3       |
| Caelo    | Black mustard seed, p... | 13358304      | 7       |
| Caelo    | Black mustard seed, p... | 14162802      | 1       |
| Caelo    | Black mustard seed, p... | 16051802      | 1       |
| Caelo    | Black mustard seed, p... | 14293702      | 6       |
| Caelo    | Black mustard seed, p... | 15131101      | 1       |
| Caelo    | Black mustard seed, p... | 14162810      | 2       |
| Caelo    | Black mustard seed, p... | 15131102      | 2       |
| Caelo    | Black mustard seed, p... | 14293701      | 2       |
| Caelo    | Black mustard seed, p... | 15131104      | 1       |
| Caelo    | Black mustard seed, p... | 15131105      | 1       |
| Caelo    | Black mustard seed, p... | 14245601      | 1       |
| Caelo    | Black mustard seed, p... | 14162810      | 3       |
| Caelo    | Black mustard seed, p... | 14162808      | 1       |
| Caelo    | Black mustard seed, p... | 15214703      | 2       |
| Caelo    | Black mustard seed, p... | 15214706      | 3       |
| Caelo    | Black mustard seed, p... | 15214708      | 3       |
| Caelo    | Black mustard seed, p... | 15214714      | 1       |
| Caelo    | Black mustard seed, p... | 14162807      | 2       |
| Caelo    | Black mustard seed, p... | 12208601      | 3       |
| Caelo    | Black mustard seed, p... | 12208602      | 7       |
| Caelo    | Black mustard seed, p... | 14293710      | 2       |
| Caelo    | Black mustard seed, p... | 12350202      | 17      |
| Caelo    | Black mustard seed, p... | 15214707      | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|--------------------------|---------------------|----------------|
| Caelo           | Black mustard seed, p... | 13097705            | 7              |
| Caelo           | Black mustard seed, p... | 13097702            | 5              |
| Caelo           | Black mustard seed, p... | 12208604            | 4              |
| Caelo           | Black mustard seed, p... | 13097701            | 14             |
| Caelo           | Black mustard seed, p... | 15214703            | 1              |
| Caelo           | Black mustard seed, p... | 15214713            | 2              |
| Caelo           | Black mustard seed, p... | 12350211            | 3              |
| Caelo           | Black mustard seed, p... | 13097706            | 3              |
| Caelo           | Black mustard seed, p... | 12350209            | 1              |
| Caelo           | Black mustard seed, p... | 12350202-3369319012 | 1              |
| Caelo           | Black mustard seed, p... | 12350205            | 3              |
| Caelo           | Black mustard seed, p... | 12009703            | 1              |
| Caelo           | Black mustard seed, p... | 14293706            | 1              |
| Caelo           | Black mustard seed, p... | 12350208            | 9              |
| Caelo           | Black mustard seed, p... | 12350207            | 5              |
| Caelo           | Black mustard seed, p... | 25011401            | 2              |
| Caelo           | Black pepper             | 12192307            | 1              |
| Caelo           | Black pepper             | 12192309            | 1              |
| Caelo           | Black pepper             | 11193911            | 1              |
| Caelo           | Black pepper             | 12192306            | 1              |
| Caelo           | Black pepper             | 12192305            | 1              |
| Caelo           | Black pepper             | 12192304            | 1              |
| Caelo           | Black pepper             | 13221110            | 1              |
| Caelo           | Blackberry leaf, cut     | 11030704            | 4              |
| Caelo           | Blackberry leaf, cut     | 11030707            | 6              |
| Caelo           | Blackberry leaf, cut     | 13101610            | 1              |
| Caelo           | Blackberry leaf, cut     | 13127901            | 1              |
| Caelo           | Blackberry leaf, cut     | 14019010            | 1              |
| Caelo           | Blackberry leaf, cut     | 11030706            | 1              |
| Caelo           | Blackberry leaf, cut     | nachprüfung         | 1              |
| Caelo           | Blackberry leaf, cut     | 15039301            | 1              |
| Caelo           | Blackberry leaf, cut     | 2110E-01512         | 1              |
| Caelo           | Blackberry leaf, cut     | 2271c120508         | 1              |
| Caelo           | Blackberry leaf, cut     | 28061202            | 1              |
| Caelo           | Blackberry leaf, cut     | 3011E-01512         | 1              |
| Caelo           | Blackberry leaf, cut     | 10136412            | 2              |
| Caelo           | Blackberry leaf, cut     | 3091303             | 1              |
| Caelo           | Blackberry leaf, cut     | 10136408            | 7              |
| Caelo           | Blackberry leaf, cut     | 10136403            | 1              |
| Caelo           | Blackberry leaf, cut     | 14111318            | 1              |
| Caelo           | Blackberry leaf, cut     | 11030701            | 2              |
| Caelo           | Blackberry leaf, cut     | 13091206            | 1              |
| Caelo           | Blackcurrant leaf, cut   | 9373913             | 1              |
| Caelo           | Blackcurrant leaf, cut   | 12168810            | 4              |
| Caelo           | Blackcurrant leaf, cut   | 12168804            | 1              |
| Caelo           | Blackcurrant leaf, cut   | 12168801            | 1              |
| Caelo           | Blackcurrant leaf, cut   | 12115902            | 2              |
| Caelo           | Blackcurrant leaf, cut   | 80558228            | 1              |
| Caelo           | Blackcurrants            | 12272804            | 3              |
| Caelo           | Blackcurrants            | 14212501            | 1              |
| Caelo           | Blackthorn flower        | 12178105            | 1              |
| Caelo           | Blackthorn flower        | 12178104            | 4              |
| Caelo           | Blackthorn flower        | 11206906            | 1              |
| Caelo           | Blackthorn flower        | 12178102            | 9              |
| Caelo           | Blackthorn flower        | 12178103            | 3              |
| Caelo           | Blackthorn flower        | 12178101            | 2              |
| Caelo           | Blessed thistle, cut     | 13025903            | 3              |
| Caelo           | Blessed thistle, cut     | 13025901            | 5              |
| Caelo           | Blessed thistle, cut     | 4743554             | 1              |
| Caelo           | Blessed thistle, cut     | 12038202            | 1              |

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| Supplier | Substance                | Batch       | Spectra |
|----------|--------------------------|-------------|---------|
| Caelo    | Blessed thistle, cut     | 10325404    | 2       |
| Caelo    | Blessed thistle, cut     | 2513A-01628 | 1       |
| Caelo    | Blessed thistle, cut     | 10325402    | 6       |
| Caelo    | Blessed thistle, cut     | 12038203    | 3       |
| Caelo    | Blessed thistle, cut     | 27111205    | 1       |
| Caelo    | Blessed thistle, cut     | 3091301     | 1       |
| Caelo    | Blessed thistle, cut     | 103225403   | 1       |
| Caelo    | Blessed thistle, cut     | 13025902    | 1       |
| Caelo    | Blessed thistle, cut     | 13389701    | 1       |
| Caelo    | Blessed thistle, cut     | 9355208     | 1       |
| Caelo    | Blue bottle flower wi... | 14323302    | 1       |
| Caelo    | Blue bottle flower wi... | 11059206    | 3       |
| Caelo    | Blue bottle flower wi... | 12060202    | 2       |
| Caelo    | Blue bottle flower wi... | 11059211    | 2       |
| Caelo    | Blue bottle flower wi... | 11059209    | 2       |
| Caelo    | Blue bottle flower wi... | 10291105    | 1       |
| Caelo    | Blue bottle flower wi... | 613Q-01456  | 1       |
| Caelo    | Blue bottle flower wi... | 12060203    | 4       |
| Caelo    | Blue bottle flower wi... | 12060205    | 4       |
| Caelo    | Blue bottle flower wi... | 12232501    | 3       |
| Caelo    | Blue bottle flower wi... | 510e-01456  | 1       |
| Caelo    | Blue bottle flower wi... | 15206601    | 1       |
| Caelo    | Bogbean leaf, cut        | 1226101     | 1       |
| Caelo    | Bogbean leaf, cut        | 1712E-01517 | 1       |
| Caelo    | Bogbean leaf, cut        | 13149001    | 1       |
| Caelo    | Bogbean leaf, cut        | 13123902    | 2       |
| Caelo    | Bogbean leaf, cut        | 13123901    | 2       |
| Caelo    | Bogbean leaf, cut        | 12226104    | 1       |
| Caelo    | Bogbean leaf, cut        | 12226101    | 1       |
| Caelo    | Boldo leaf, cut          | 11016508    | 1       |
| Caelo    | Boldo leaf, cut          | 11016511    | 1       |
| Caelo    | Boldo leaf, cut          | 655456      | 1       |
| Caelo    | Boldo leaf, cut          | 11016502    | 1       |
| Caelo    | Boldo leaf, cut          | 11016506    | 2       |
| Caelo    | Boldo leaf, cut          | 11016509    | 1       |
| Caelo    | Boldo leaf, cut          | 12227005    | 2       |
| Caelo    | Boldo leaf, cut          | 12227004    | 1       |
| Caelo    | Boldo leaf, cut          | 12064306    | 1       |
| Caelo    | Boldo leaf, cut          | 12064305    | 1       |
| Caelo    | Boldo leaf, cut          | 12064303    | 1       |
| Caelo    | Bucho leaf               | 13056601    | 3       |
| Caelo    | Bucho leaf               | 13056605    | 1       |
| Caelo    | Bucho leaf               | 13056602    | 2       |
| Caelo    | Buckwheat herb, cut      | 11212807    | 2       |
| Caelo    | Buckwheat herb, cut      | 5111302     | 1       |
| Caelo    | Buckwheat herb, cut      | 2051303     | 1       |
| Caelo    | Buckwheat herb, cut      | 11212612    | 1       |
| Caelo    | Buckwheat herb, cut      | 11212809    | 1       |
| Caelo    | Buckwheat herb, cut      | 11212808    | 2       |
| Caelo    | Buckwheat herb, cut      | 11212810    | 1       |
| Caelo    | Buckwheat herb, cut      | 13193203    | 1       |
| Caelo    | Buckwheat herb, cut      | 13051303    | 1       |
| Caelo    | Buckwheat herb, cut      | 11212817    | 6       |
| Caelo    | Buckwheat herb, cut      | 11212815    | 2       |
| Caelo    | Buckwheat herb, cut      | 11212814    | 2       |
| Caelo    | Buckwheat herb, cut      | 30041301    | 1       |
| Caelo    | Buckwheat herb, cut      | 11212812    | 1       |
| Caelo    | Burdock root, cut        | 1100801     | 1       |
| Caelo    | Burdock root, cut        | 12295807    | 1       |
| Caelo    | Burdock root, cut        | 107063      | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b> | <b>Spectra</b> |
|-----------------|--------------------------|--------------|----------------|
| Caelo           | Burdock root, cut        | 12295804     | 1              |
| Caelo           | Burdock root, cut        | 1007306      | 1              |
| Caelo           | Burdock root, cut        | 12295808     | 2              |
| Caelo           | Burdock root, cut        | 13122801     | 2              |
| Caelo           | Burdock root, cut        | 11100802     | 1              |
| Caelo           | Burdock root, cut        | 12295801     | 2              |
| Caelo           | Burdock root, cut        | 13122802     | 1              |
| Caelo           | Burdock root, cut        | 12295802     | 4              |
| Caelo           | Burdock root, cut        | 12295805     | 2              |
| Caelo           | Burdock root, cut        | 11100801     | 2              |
| Caelo           | Burdock root, cut        | 10073208     | 1              |
| Caelo           | Burdock root, cut        | 12295803     | 3              |
| Caelo           | Burnet root              | 12027413     | 1              |
| Caelo           | Burnet root              | 12027409     | 1              |
| Caelo           | Burnet root              | 12027405     | 4              |
| Caelo           | Burnet root              | 10219402     | 1              |
| Caelo           | Burnet root              | 8111203      | 1              |
| Caelo           | Burnet root              | nachprüfung  | 2              |
| Caelo           | Burnet root              | 12027403     | 1              |
| Caelo           | Burnet root              | 12027411     | 4              |
| Caelo           | Burnet root              | 12027410     | 3              |
| Caelo           | Caffeine citrate         | 11F21-N05    | 1              |
| Caelo           | Calcium chloride dihy... | 11230921     | 2              |
| Caelo           | Calcium chloride dihy... | 11230915     | 1              |
| Caelo           | Calcium chloride dihy... | 12238401     | 2              |
| Caelo           | Calcium chloride dihy... | 12341401     | 1              |
| Caelo           | Calcium chloride dihy... | 12341404     | 2              |
| Caelo           | Calcium chloride dihy... | 12341409     | 1              |
| Caelo           | Calcium chloride dihy... | 12B09-N11    | 1              |
| Caelo           | Calcium chloride dihy... | 12341406     | 1              |
| Caelo           | Calcium chloride dihy... | 8237314      | 1              |
| Caelo           | Calcium hydrogen phos... | 12212804     | 8              |
| Caelo           | Calcium hydrogen phos... | 10135222     | 1              |
| Caelo           | Calcium hydrogen phos... | 12212809     | 2              |
| Caelo           | Calcium hydrogen phos... | 12212807     | 1              |
| Caelo           | Calcium hydrogen phos... | 11287509     | 2              |
| Caelo           | Calcium hydrogen phos... | 12212822     | 1              |
| Caelo           | Calcium hydrogen phos... | 12212806     | 1              |
| Caelo           | Calcium hydrogen phos... | 13170701     | 5              |
| Caelo           | Calcium hydrogen phos... | 10135223     | 1              |
| Caelo           | Calcium hydrogen phos... | 12212816     | 1              |
| Caelo           | Calcium hydrogen phos... | 14011401     | 1              |
| Caelo           | Calcium hydrogen phos... | 11287510     | 1              |
| Caelo           | Calcium hydrogen phos... | 14085301     | 1              |
| Caelo           | Calcium hydrogen phos... | 11287503     | 2              |
| Caelo           | Calcium hydrogen phos... | 101352009    | 1              |
| Caelo           | Calcium hydrogen phos... | 10135201     | 1              |
| Caelo           | Calcium hydrogen phos... | 10135216     | 1              |
| Caelo           | Calcium hydrogen phos... | 12212812     | 2              |
| Caelo           | Calcium hydrogen phos... | 13170704     | 2              |
| Caelo           | Calcium hydrogen phos... | 12212813     | 1              |
| Caelo           | Calcium sulfate dihyd... | 10132403     | 1              |
| Caelo           | Calcium sulfate dihyd... | 11164005     | 1              |
| Caelo           | Calcium sulfate dihyd... | 12257701     | 1              |
| Caelo           | Calcium sulfate dihyd... | 12257703     | 4              |
| Caelo           | Calcium sulfate dihyd... | 12316301     | 2              |
| Caelo           | Calcium sulfate hemih... | 9246320      | 1              |
| Caelo           | Calcium sulfate hemih... | 9246322      | 2              |
| Caelo           | Calendula flower         | 13235503     | 3              |
| Caelo           | Calendula flower         | 12221705     | 1              |

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| Supplier | Substance             | Batch               | Spectra |
|----------|-----------------------|---------------------|---------|
| Caelo    | Calendula flower      | 12221706            | 2       |
| Caelo    | Calendula flower      | 12221708            | 3       |
| Caelo    | Calendula flower      | 12221510-3356319071 | 1       |
| Caelo    | Calendula flower      | 12221510-3435311151 | 1       |
| Caelo    | Calendula flower      | 12221709            | 1       |
| Caelo    | Calendula flower      | 13235502            | 3       |
| Caelo    | Calendula flower      | 122221707           | 1       |
| Caelo    | Calendula flower      | 12221513            | 1       |
| Caelo    | Calendula flower      | 12221511            | 1       |
| Caelo    | Calendula flower      | 12221710            | 1       |
| Caelo    | Calendula flower      | 13235501            | 1       |
| Caelo    | Calendula flower      | 12221508            | 1       |
| Caelo    | Calendula flower      | 15291501            | 1       |
| Caelo    | Calendula flower, cut | 1187612             | 3       |
| Caelo    | Calendula flower, cut | 12221601            | 6       |
| Caelo    | Calendula flower, cut | 18121301            | 1       |
| Caelo    | Calendula flower, cut | 15040301            | 1       |
| Caelo    | Calendula flower, cut | 13235501            | 4       |
| Caelo    | Calendula flower, cut | 11187616            | 1       |
| Caelo    | Calendula flower, cut | 13235502            | 11      |
| Caelo    | Calendula flower, cut | 10117006            | 1       |
| Caelo    | Calendula flower, cut | 13410202            | 2       |
| Caelo    | Calendula flower, cut | 12221708            | 14      |
| Caelo    | Calendula flower, cut | 1325502             | 1       |
| Caelo    | Calendula flower, cut | 12221710            | 2       |
| Caelo    | Calendula flower, cut | 9121303             | 1       |
| Caelo    | Calendula flower, cut | 9112013C            | 1       |
| Caelo    | Calendula flower, cut | AKD1                | 1       |
| Caelo    | Calendula flower, cut | 13235505            | 1       |
| Caelo    | Calendula flower, cut | 31121202            | 1       |
| Caelo    | Calendula flower, cut | 8041302             | 1       |
| Caelo    | Calendula flower, cut | 295556              | 1       |
| Caelo    | Calendula flower, cut | 5021305             | 1       |
| Caelo    | Calendula flower, cut | 3061301             | 1       |
| Caelo    | Calendula flower, cut | 122221704           | 1       |
| Caelo    | Calendula flower, cut | 12221705            | 5       |
| Caelo    | Calendula flower, cut | 11221407            | 2       |
| Caelo    | Calendula flower, cut | 11187607            | 4       |
| Caelo    | Calendula flower, cut | 12221707            | 3       |
| Caelo    | Calendula flower, cut | 11221409            | 2       |
| Caelo    | Calendula flower, cut | 12221507            | 1       |
| Caelo    | Calendula flower, cut | 12221701            | 2       |
| Caelo    | Calendula flower, cut | 11187611            | 5       |
| Caelo    | Calendula flower, cut | 12221503            | 1       |
| Caelo    | Calendula flower, cut | 12221502            | 2       |
| Caelo    | Calendula flower, cut | 11187605            | 1       |
| Caelo    | Calendula flower, cut | 11187610            | 5       |
| Caelo    | Calendula flower, cut | 10117004            | 3       |
| Caelo    | Calendula flower, cut | 10291904            | 4       |
| Caelo    | Calendula flower, cut | 11187612            | 16      |
| Caelo    | Calendula flower, cut | 27101201            | 1       |
| Caelo    | Calendula flower, cut | 13235506            | 2       |
| Caelo    | Calendula flower, cut | 12221704            | 15      |
| Caelo    | Calendula flower, cut | 22061203            | 1       |
| Caelo    | Calendula flower, cut | 21091301            | 1       |
| Caelo    | Calendula flower, cut | 19111206            | 1       |
| Caelo    | Calendula flower, cut | 12071201            | 1       |
| Caelo    | Calendula flower, cut | 12221506            | 1       |
| Caelo    | Caraway fruit         | 1226608             | 1       |
| Caelo    | Caraway fruit         | 13041901            | 1       |

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| <b>Supplier</b> | <b>Substance</b>       | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|------------------------|---------------------|----------------|
| Caelo           | Caraway fruit          | 1509101             | 1              |
| Caelo           | Caraway fruit          | 13306002            | 8              |
| Caelo           | Caraway fruit          | 12345               | 1              |
| Caelo           | Caraway fruit          | 12228601            | 1              |
| Caelo           | Caraway fruit          | 13041903            | 1              |
| Caelo           | Caraway fruit          | 12343403            | 1              |
| Caelo           | Caraway fruit          | 12226614            | 5              |
| Caelo           | Caraway fruit          | 6111206             | 1              |
| Caelo           | Caraway fruit          | 12226608            | 4              |
| Caelo           | Caraway fruit          | 11378309            | 1              |
| Caelo           | Caraway fruit          | 12226603            | 9              |
| Caelo           | Caraway fruit          | 11003211            | 1              |
| Caelo           | Caraway fruit          | 11003201            | 1              |
| Caelo           | Caraway fruit          | 10111213            | 1              |
| Caelo           | Caraway fruit          | 12226604            | 5              |
| Caelo           | Caraway fruit          | 12226605            | 4              |
| Caelo           | Caraway fruit          | 12226606            | 2              |
| Caelo           | Caraway fruit          | 9267815             | 1              |
| Caelo           | Caraway fruit          | 811E-01537          | 1              |
| Caelo           | Caraway fruit          | 27121202            | 1              |
| Caelo           | Caraway fruit          | 610E-01537          | 1              |
| Caelo           | Caraway fruit          | 4061303             | 1              |
| Caelo           | Caraway fruit          | 12226611            | 3              |
| Caelo           | Caraway fruit          | 12226612            | 10             |
| Caelo           | Caraway fruit          | 1222608             | 1              |
| Caelo           | Caraway fruit          | 2103311537          | 1              |
| Caelo           | Caraway fruit          | 13306008            | 1              |
| Caelo           | Caraway fruit          | 13306003            | 1              |
| Caelo           | Caraway fruit          | 12226601            | 1              |
| Caelo           | Caraway fruit          | 15097108            | 4              |
| Caelo           | Caraway fruit          | 15097109            | 2              |
| Caelo           | Caraway fruit          | 16308503            | 1              |
| Caelo           | Caraway fruit          | 15409105            | 1              |
| Caelo           | Caraway fruit          | 15409104            | 1              |
| Caelo           | Caraway fruit          | 11003207            | 1              |
| Caelo           | Caraway fruit          | 11003217            | 7              |
| Caelo           | Caraway fruit          | 12226501            | 9              |
| Caelo           | Caraway fruit          | 413M                | 1              |
| Caelo           | Caraway fruit          | 150979101           | 1              |
| Caelo           | Caraway fruit          | 15097116            | 1              |
| Caelo           | Caraway fruit          | 13091401            | 1              |
| Caelo           | Caraway fruit          | 15097115            | 3              |
| Caelo           | Caraway fruit          | 15097110            | 1              |
| Caelo           | Caraway fruit          | 15097107            | 2              |
| Caelo           | Caraway fruit          | 15097103            | 2              |
| Caelo           | Caraway fruit          | 15097101            | 10             |
| Caelo           | Caraway fruit          | 13397105            | 9              |
| Caelo           | Caraway fruit          | 13397104            | 3              |
| Caelo           | Caraway fruit          | 13397102            | 2              |
| Caelo           | Caraway fruit          | 13367102            | 1              |
| Caelo           | Caraway fruit          | 13306006            | 5              |
| Caelo           | Caraway fruit          | 13306005            | 3              |
| Caelo           | Caraway fruit          | 13306004            | 1              |
| Caelo           | Caraway fruit          | 15097111            | 1              |
| Caelo           | Caraway fruit          | 12226504            | 1              |
| Caelo           | Caraway fruit, pounded | 14160401            | 1              |
| Caelo           | Cardamom fruit         | 13260502-3537411072 | 1              |
| Caelo           | Cardamom fruit         | 11309110            | 3              |
| Caelo           | Cardamom fruit         | 13026003            | 1              |
| Caelo           | Castoreum, powdered    | o810I-01236         | 1              |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Cayenne pepper, powde... | 13205106            | 1       |
| Caelo    | Celery root, cut         | 12319108            | 1       |
| Caelo    | Celery root, cut         | 12319107            | 1       |
| Caelo    | Celery root, cut         | 10270009            | 1       |
| Caelo    | Celery root, cut         | 12319105            | 2       |
| Caelo    | Celery root, cut         | 10270012            | 1       |
| Caelo    | Centaury, cut            | 11097611            | 1       |
| Caelo    | Centaury, cut            | 11097608            | 1       |
| Caelo    | Centaury, cut            | 12379601            | 1       |
| Caelo    | Centaury, cut            | 12268605            | 4       |
| Caelo    | Centaury, cut            | 11097602            | 2       |
| Caelo    | Centaury, cut            | 8021302             | 1       |
| Caelo    | Centaury, cut            | 15224102            | 1       |
| Caelo    | Centaury, cut            | 11097605            | 3       |
| Caelo    | Centaury, cut            | 12268608            | 13      |
| Caelo    | Centaury, cut            | 3711B120628         | 1       |
| Caelo    | Centaury, cut            | 1523                | 1       |
| Caelo    | Centaury, cut            | 11097612            | 17      |
| Caelo    | Centaury, cut            | 12268606            | 13      |
| Caelo    | Centaury, cut            | 1212E-01629         | 1       |
| Caelo    | Centaury, cut            | 12268601            | 3       |
| Caelo    | Centaury, cut            | 12268602            | 18      |
| Caelo    | Centaury, cut            | 11097609            | 6       |
| Caelo    | Ceylon cinnamon, fine... | abcdef              | 1       |
| Caelo    | Ceylonese Cinnamon, p... | 12242815            | 1       |
| Caelo    | Ceylonese Cinnamon, p... | 11306016            | 1       |
| Caelo    | Ceylonese Cinnamon, p... | 12242806            | 2       |
| Caelo    | Ceylonese Cinnamon, p... | 12242818            | 1       |
| Caelo    | Chelidonium majus her... | 311092              | 1       |
| Caelo    | Chickweed, cut           | 13040502-3283310662 | 1       |
| Caelo    | Chickweed, cut           | 13040502            | 2       |
| Caelo    | Chickweed, cut           | 13254403            | 2       |
| Caelo    | Chickweed, cut           | 13254401            | 1       |
| Caelo    | Chickweed, cut           | 13040504            | 1       |
| Caelo    | Chickweed, cut           | 13040501            | 1       |
| Caelo    | Chickweed, cut           | 14212403            | 1       |
| Caelo    | Chickweed, cut           | 10359117            | 2       |
| Caelo    | Chickweed, cut           | 14212411            | 1       |
| Caelo    | Chickweed, cut           | 4551B130902         | 1       |
| Caelo    | Chickweed, cut           | 211e-01686          | 1       |
| Caelo    | Chickweed, cut           | 13040503            | 1       |
| Caelo    | Chickweed, cut           | 10359116            | 1       |
| Caelo    | Chickweed, cut           | 13254404            | 1       |
| Caelo    | Chicory herb, cut        | nachprüfung         | 1       |
| Caelo    | Chicory herb, cut        | 14031315            | 1       |
| Caelo    | Chicory herb, cut        | 12034301            | 4       |
| Caelo    | Chicory herb, cut        | 12354306            | 1       |
| Caelo    | Chicory herb, cut        | 12034303            | 4       |
| Caelo    | Chicory herb, cut        | 12354302            | 5       |
| Caelo    | Chicory herb, cut        | 12369101            | 5       |
| Caelo    | Chicory herb, cut        | 12034302            | 3       |
| Caelo    | Chicory herb, cut        | 10325606            | 1       |
| Caelo    | Chicory herb, cut        | 12369102            | 3       |
| Caelo    | Chicory herb, cut        | 12354304            | 1       |
| Caelo    | Chicory root, cut        | 6221As101202        | 1       |
| Caelo    | Chicory root, cut        | 913Q-02134          | 1       |
| Caelo    | Chicory root, cut        | 91338319            | 1       |
| Caelo    | Chicory root, cut        | 11374506            | 2       |
| Caelo    | Chicory root, cut        | 11374504            | 3       |
| Caelo    | Chicory root, cut        | 11081803            | 1       |

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| Supplier | Substance                | Batch           | Spectra |
|----------|--------------------------|-----------------|---------|
| Caelo    | Chicory root, cut        | 11374510        | 2       |
| Caelo    | Cinchona bark, cut       | 11238512        | 1       |
| Caelo    | Cinchona bark, cut       | 10381906        | 1       |
| Caelo    | Cinchona bark, cut       | 14009305        | 1       |
| Caelo    | Cinnamon rods (Ceylon... | 12148904        | 1       |
| Caelo    | Cinnamon rods (Ceylon... | 13231601        | 2       |
| Caelo    | Cinnamon, cut            | 11357909        | 2       |
| Caelo    | Cinnamon, cut            | 25111307        | 1       |
| Caelo    | Cinnamon, cut            | 13304414        | 1       |
| Caelo    | Cinnamon, cut            | 13304415        | 1       |
| Caelo    | Cinnamon, cut            | 13304401        | 2       |
| Caelo    | Cinnamon, cut            | 12309909        | 1       |
| Caelo    | Cinnamon, cut            | 12309908        | 1       |
| Caelo    | Cinnamon, cut            | 13304402        | 2       |
| Caelo    | Cinnamon, cut            | 12309902        | 3       |
| Caelo    | Cinnamon, cut            | 11357912        | 2       |
| Caelo    | Cinnamon, cut            | 15151905        | 1       |
| Caelo    | Cinnamon, cut            | 13231603        | 1       |
| Caelo    | Clove                    | 14057602        | 1       |
| Caelo    | Clove                    | 2010i-01450     | 1       |
| Caelo    | Clove                    | 12266505        | 1       |
| Caelo    | Clove                    | 12095807        | 4       |
| Caelo    | Clove                    | 12095802        | 1       |
| Caelo    | Clove                    | 11233305        | 1       |
| Caelo    | Clove                    | 5398872         | 1       |
| Caelo    | Clove                    | 13371309        | 1       |
| Caelo    | Clove                    | 13371306        | 1       |
| Caelo    | Clove                    | 12095806        | 2       |
| Caelo    | Clove, powdered (spice)  | 14180001        | 1       |
| Caelo    | Clove, powdered (spice)  | 12355303        | 1       |
| Caelo    | Cocaine hydrochloride    | 13259305        | 1       |
| Caelo    | Cocaine hydrochloride    | 14069209        | 1       |
| Caelo    | Cocaine hydrochloride    | 16142705        | 1       |
| Caelo    | Cocaine hydrochloride    | 12329103        | 1       |
| Caelo    | Cocaine hydrochloride    | 13259306        | 1       |
| Caelo    | Cocaine hydrochloride    | C17H22CIN04     | 1       |
| Caelo    | Cocaine hydrochloride    | 13112102        | 1       |
| Caelo    | Cocoa bark, cut          | 19011303        | 1       |
| Caelo    | Cocoa bark, cut          | 12126910        | 1       |
| Caelo    | Cocoa bark, cut          | 12126907        | 1       |
| Caelo    | Cocoa bark, cut          | 12126905        | 2       |
| Caelo    | Cocoa bark, cut          | 12126901        | 1       |
| Caelo    | Cocoa bark, cut          | nachprüfung     | 1       |
| Caelo    | Cocoa bark, cut          | 1216907         | 1       |
| Caelo    | Codeine phosphate hem... | 15219805        | 1       |
| Caelo    | Codeine phosphate hem... | 1427910         | 1       |
| Caelo    | Codeine phosphate hem... | 14275910        | 1       |
| Caelo    | Codeine phosphate hem... | 13G03-N10       | 1       |
| Caelo    | Codeine phosphate hem... | 15350703        | 2       |
| Caelo    | Coltsfoot leaf, cut      | 2021B130227     | 16      |
| Caelo    | Coltsfoot leaf, cut      | 23041302        | 1       |
| Caelo    | Coltsfoot leaf, cut      | 25021304        | 1       |
| Caelo    | Coltsfoot leaf, cut      | 2021B121204     | 16      |
| Caelo    | Coltsfoot leaf, cut      | Int.Ch:Now16081 | 1       |
| Caelo    | Comfrey root             | 4112E-02135     | 1       |
| Caelo    | Comfrey root             | 2711Q-02135     | 1       |
| Caelo    | Comfrey root             | 116053          | 1       |
| Caelo    | Common broom herb, cut   | 12358802        | 1       |
| Caelo    | Common broom herb, cut   | 11132209        | 1       |
| Caelo    | Common broom herb, cut   | 4412Q-01680     | 1       |

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| Supplier | Substance                | Batch       | Spectra |
|----------|--------------------------|-------------|---------|
| Caelo    | Common broom herb, cut   | 13241601    | 1       |
| Caelo    | Common broom herb, cut   | 12358805    | 1       |
| Caelo    | Common broom herb, cut   | 12358804    | 3       |
| Caelo    | Common wormwood herb,... | 4712A-01620 | 1       |
| Caelo    | Common wormwood herb,... | 12016705    | 9       |
| Caelo    | Common wormwood herb,... | 12016702    | 2       |
| Caelo    | Common wormwood herb,... | 1238701     | 1       |
| Caelo    | Common wormwood herb,... | 3591A100315 | 1       |
| Caelo    | Common wormwood herb,... | 18031302    | 1       |
| Caelo    | Common wormwood herb,... | 1081301     | 1       |
| Caelo    | Common wormwood herb,... | 10355329    | 1       |
| Caelo    | Common wormwood herb,... | 14360605    | 1       |
| Caelo    | Common wormwood herb,... | 10357806    | 1       |
| Caelo    | Common wormwood herb,... | 12382706    | 1       |
| Caelo    | Common wormwood herb,... | 3591A110119 | 4       |
| Caelo    | Common wormwood herb,... | 9355403     | 1       |
| Caelo    | Common wormwood herb,... | 12382705    | 2       |
| Caelo    | Common wormwood herb,... | 12382702    | 11      |
| Caelo    | Common wormwood herb,... | 12382701    | 8       |
| Caelo    | Common wormwood herb,... | 12016711    | 4       |
| Caelo    | Common wormwood herb,... | 12016709    | 3       |
| Caelo    | Common wormwood herb,... | 12016701    | 1       |
| Caelo    | Copper (II) sulfate p... | 12157107    | 1       |
| Caelo    | Copper (II) sulfate p... | 12135001    | 1       |
| Caelo    | Copper (II) sulfate p... | 10L15-N06   | 1       |
| Caelo    | Copper (II) sulfate p... | 3411M-01317 | 1       |
| Caelo    | Copper (II) sulfate p... | 3211M-01317 | 1       |
| Caelo    | Copper (II) sulfate p... | 2913U-01317 | 1       |
| Caelo    | Coriander                | 12080905    | 1       |
| Caelo    | Coriander                | 4091305     | 1       |
| Caelo    | Coriander                | 12080901    | 2       |
| Caelo    | Coriander                | 12080906    | 2       |
| Caelo    | Coriander                | 14031316    | 1       |
| Caelo    | Coriander                | 16010201    | 1       |
| Caelo    | Coriander                | 9285707     | 1       |
| Caelo    | Coriander                | 13010304    | 2       |
| Caelo    | Coriander                | 13010306    | 2       |
| Caelo    | Coriander                | 27061305    | 1       |
| Caelo    | Cottonwood bud           | 70864257    | 1       |
| Caelo    | Cottonwood bud           | nachprüfung | 1       |
| Caelo    | Cottonwood bud           | 12027506    | 1       |
| Caelo    | Cottonwood bud           | 12027504    | 1       |
| Caelo    | Couch grass rhizome, ... | 3712I-02180 | 1       |
| Caelo    | Couch grass rhizome, ... | nachprüfung | 1       |
| Caelo    | Couch grass rhizome, ... | 10349704    | 1       |
| Caelo    | Couch grass rhizome, ... | 10349705    | 2       |
| Caelo    | Couch grass rhizome, ... | 12186701    | 1       |
| Caelo    | Couch grass rhizome, ... | 12186705    | 1       |
| Caelo    | Couch grass rhizome, ... | 12186817    | 3       |
| Caelo    | Couch grass rhizome, ... | 10049618    | 2       |
| Caelo    | Couch grass rhizome, ... | 10049614    | 1       |
| Caelo    | Couch grass rhizome, ... | 10049606    | 1       |
| Caelo    | Cowberry leaf, cut       | 12150205    | 1       |
| Caelo    | Cowberry leaf, cut       | 12105203    | 1       |
| Caelo    | Cowberry leaf, cut       | 12105201    | 1       |
| Caelo    | Cowberry leaf, cut       | 11334302    | 1       |
| Caelo    | Daisy flower             | 11103203    | 3       |
| Caelo    | Daisy flower             | 11103201    | 2       |
| Caelo    | Daisy flower             | 12133705    | 1       |
| Caelo    | Daisy flower             | 1210a120215 | 2       |

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| Supplier | Substance                 | Batch               | Spectra |
|----------|---------------------------|---------------------|---------|
| Caelo    | Daisy flower              | 12133703            | 1       |
| Caelo    | Daisy flower              | 11068308            | 1       |
| Caelo    | Damiana leaf, cut         | 11026607            | 2       |
| Caelo    | Damiana leaf, cut         | 12064103            | 3       |
| Caelo    | Damiana leaf, cut         | 12330401            | 4       |
| Caelo    | Damiana leaf, cut         | 12330402            | 10      |
| Caelo    | Damiana leaf, cut         | 12330403            | 2       |
| Caelo    | Damiana leaf, cut         | 12330407            | 2       |
| Caelo    | Dandelion herb with r...  | 806212165           | 1       |
| Caelo    | Dandelion herb with r...  | 10121602            | 1       |
| Caelo    | Dandelion herb with r...  | 8111205             | 1       |
| Caelo    | Dandelion herb with r...  | 12236001            | 4       |
| Caelo    | Dandelion herb with r...  | 12236003            | 5       |
| Caelo    | Dandelion herb with r...  | 1103011             | 1       |
| Caelo    | Dandelion herb with r...  | 11030314            | 6       |
| Caelo    | Dandelion herb with r...  | 13019802-3395310101 | 1       |
| Caelo    | Dandelion herb with r...  | 12236002            | 10      |
| Caelo    | Dandelion herb with r...  | 11030309            | 5       |
| Caelo    | Dandelion herb with r...  | 11030313            | 3       |
| Caelo    | Dandelion herb with r...  | 11371903            | 1       |
| Caelo    | Dandelion herb with r...  | 10121610            | 1       |
| Caelo    | Dandelion herb with r...  | 13019802            | 22      |
| Caelo    | Dandelion herb with r...  | Ch.-B.:13019802     | 1       |
| Caelo    | Dandelion herb with r...  | 13108802            | 13      |
| Caelo    | Dandelion herb with r...  | 13108801            | 4       |
| Caelo    | Dandelion herb with r...  | Int.Ch:318090       | 1       |
| Caelo    | Dandelion herb with r...  | 13199202            | 2       |
| Caelo    | Dandelion herb with r...  | 13317903            | 1       |
| Caelo    | Dandelion herb with r...  | 17121305            | 1       |
| Caelo    | Dandelion herb with r...  | 20111202            | 1       |
| Caelo    | Dandelion herb with r...  | 2112122165          | 1       |
| Caelo    | Dandelion herb with r...  | 6611B100902         | 1       |
| Caelo    | Dandelion herb with r...  | 7341703             | 1       |
| Caelo    | Dandelion herb with r...  | 13019805            | 3       |
| Caelo    | Dandelion herb with r...  | 13019801            | 6       |
| Caelo    | Dandelion herb with r...  | 7131-02165          | 1       |
| Caelo    | Dandelion herb with r...  | 13018902            | 1       |
| Caelo    | Dandelion herb with r...  | 12252101            | 1       |
| Caelo    | Dandelion herb with r...  | 12236005            | 7       |
| Caelo    | Dandelion herb without... | 13091305            | 1       |
| Caelo    | Dandelion herb without... | 11371907            | 1       |
| Caelo    | Dandelion herb without... | 11371904            | 3       |
| Caelo    | Dandelion herb without... | 11371902            | 2       |
| Caelo    | Dandelion herb without... | 1127102             | 1       |
| Caelo    | Dandelion herb without... | 11217109            | 2       |
| Caelo    | Dandelion herb without... | 9011403             | 1       |
| Caelo    | Dandelion herb without... | 7031305             | 1       |
| Caelo    | Dandelion herb without... | 11217107            | 1       |
| Caelo    | Dandelion herb without... | 1137907             | 1       |
| Caelo    | Dandelion herb without... | 107063              | 1       |
| Caelo    | Dandelion herb without... | 11030311            | 1       |
| Caelo    | Dandelion root, cut       | 15407703            | 3       |
| Caelo    | Dandelion root, cut       | 10024710            | 1       |
| Caelo    | Dandelion root, cut       | 11003308            | 2       |
| Caelo    | Dandelion root, cut       | 8120                | 1       |
| Caelo    | Dandelion root, cut       | 11003306            | 1       |
| Caelo    | Dandelion root, cut       | 11003309            | 1       |
| Caelo    | Dandelion root, cut       | 11003312            | 1       |
| Caelo    | Dandelion root, cut       | 1225101             | 1       |
| Caelo    | Dandelion root, cut       | 12363102            | 3       |

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| Supplier | Substance                | Batch        | Spectra |
|----------|--------------------------|--------------|---------|
| Caelo    | Dandelion root, cut      | 12363103     | 1       |
| Caelo    | Dandelion root, cut      | 16161303     | 1       |
| Caelo    | Dandelion root, cut      | 12363104     | 4       |
| Caelo    | Dandelion root, cut      | 12363106     | 1       |
| Caelo    | Dandelion root, cut      | 13329705     | 1       |
| Caelo    | Dandelion root, cut      | 12363107     | 1       |
| Caelo    | Dandelion root, cut      | 12363108     | 2       |
| Caelo    | Dandelion root, cut      | 12363109     | 4       |
| Caelo    | Dandelion root, cut      | 12363110     | 1       |
| Caelo    | Dandelion root, cut      | 14166504     | 1       |
| Caelo    | Dandelion root, cut      | 6621A-120606 | 1       |
| Caelo    | Dandelion root, cut      | 13329704     | 1       |
| Caelo    | Dandelion root, cut      | 12363105     | 1       |
| Caelo    | Dandelion root, cut      | 14166502     | 1       |
| Caelo    | Dandelion root, cut      | 15407703     | 1       |
| Caelo    | Dandelion root, cut      | 14376602     | 1       |
| Caelo    | Dandelion root, cut      | 12367916     | 1       |
| Caelo    | Dandelion root, cut      | 14376603     | 1       |
| Caelo    | Dandelion root, cut      | 13329702     | 10      |
| Caelo    | Dandelion root, cut      | 14166504     | 1       |
| Caelo    | Dandelion root, cut      | 11003307     | 1       |
| Caelo    | Devil's claw root        | 12031801     | 1       |
| Caelo    | Devil's claw root        | 12031803     | 2       |
| Caelo    | Devil's claw root        | 12031806     | 1       |
| Caelo    | Devil's claw root        | 12031810     | 1       |
| Caelo    | Devil's claw root        | 12031811     | 1       |
| Caelo    | Devil's claw root        | 6331B110426  | 2       |
| Caelo    | Dexamphetamine sulfate   | C9H13N14     | 1       |
| Caelo    | Dihydrocodeine hydrog... | 13267603     | 1       |
| Caelo    | Dihydrocodeine hydrog... | 13267604     | 2       |
| Caelo    | Dihydrocodeine hydrog... | 15295903     | 2       |
| Caelo    | Dihydrocodeine hydrog... | 15295905     | 2       |
| Caelo    | Dihydrocodeine hydrog... | 15295907     | 1       |
| Caelo    | Dihydrocodeine hydrog... | 12142503     | 2       |
| Caelo    | Dihydrocodeine hydrog... | 12142508     | 2       |
| Caelo    | Dihydrocodeine hydrog... | 13267608     | 1       |
| Caelo    | Dill fruit               | 12342908     | 3       |
| Caelo    | Dill fruit               | 12342909     | 5       |
| Caelo    | Dill fruit               | 12289901     | 1       |
| Caelo    | Dill fruit               | 16348701     | 1       |
| Caelo    | Dill fruit               | 9189003      | 1       |
| Caelo    | Dill fruit               | 2413M-01526  | 1       |
| Caelo    | Dill fruit               | 12342901     | 3       |
| Caelo    | Dill fruit               | 12038304     | 4       |
| Caelo    | Dill fruit               | 12342903     | 1       |
| Caelo    | Dill fruit               | 12038302     | 2       |
| Caelo    | Dill fruit               | 12342904     | 6       |
| Caelo    | Dill fruit               | 12342906     | 3       |
| Caelo    | Dill herb, cut           | 13007608     | 1       |
| Caelo    | Dill herb, cut           | 13007601     | 1       |
| Caelo    | Dill herb, cut           | 13007605     | 1       |
| Caelo    | Dill herb, cut           | 11295109     | 1       |
| Caelo    | Dill herb, cut           | 13007602     | 1       |
| Caelo    | Dithranole               | 13120702     | 1       |
| Caelo    | Dithranole               | 120302502    | 2       |
| Caelo    | Dithranole               | 12375302     | 4       |
| Caelo    | Dithranole               | 12236811     | 4       |
| Caelo    | Dithranole               | 120302501    | 1       |
| Caelo    | Dithranole               | 12375305     | 1       |
| Caelo    | Dithranole               | 12375402     | 1       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Dithranole               | 12375403            | 1       |
| Caelo    | Dithranole               | 13120503            | 1       |
| Caelo    | Dithranole               | 1212I-01274         | 1       |
| Caelo    | Dithranole               | 120145041 . 2013    | 1       |
| Caelo    | Dithranole               | 12014504            | 2       |
| Caelo    | Dithranole               | 13120504            | 1       |
| Caelo    | Dithranole               | 11064501            | 1       |
| Caelo    | Dithranole               | 13120502            | 1       |
| Caelo    | Dithranole               | 12375601            | 1       |
| Caelo    | Dithranole               | 12236809            | 1       |
| Caelo    | Dithranole               | 12014502            | 1       |
| Caelo    | Dithranole               | 27111206            | 1       |
| Caelo    | Dithranole               | APDT/3652011D       | 1       |
| Caelo    | Dry beads Caelo ora...   | 12382204            | 1       |
| Caelo    | Dry beads Caelo ora...   | 11005811            | 1       |
| Caelo    | Dry beads Caelo ora...   | 11005813            | 1       |
| Caelo    | Echinacea pallida roo... | 11115206            | 1       |
| Caelo    | Echinacea pallida roo... | 12244504            | 1       |
| Caelo    | Elder berries            | 12267801            | 1       |
| Caelo    | Elder flower, rubbed     | 9297412             | 1       |
| Caelo    | Elder flower, rubbed     | 10291312            | 4       |
| Caelo    | Elder flower, rubbed     | 9297417             | 2       |
| Caelo    | Elder flower, rubbed     | 1029310             | 1       |
| Caelo    | Elder flower, rubbed     | 10291301            | 1       |
| Caelo    | Elder flower, rubbed     | 31051301            | 1       |
| Caelo    | Elder flower, rubbed     | 5122013d            | 1       |
| Caelo    | Elder flower, rubbed     | 12221902            | 10      |
| Caelo    | Elder flower, rubbed     | 10291310            | 6       |
| Caelo    | Elder flower, rubbed     | 12221904-3360319071 | 1       |
| Caelo    | Elder flower, rubbed     | 12221905            | 9       |
| Caelo    | Elder flower, rubbed     | 213E-01471          | 1       |
| Caelo    | Elder flower, rubbed     | 12221906            | 1       |
| Caelo    | Elder flower, rubbed     | 10291308            | 2       |
| Caelo    | Elder flower, rubbed     | 10291304            | 1       |
| Caelo    | Elder flower, rubbed     | 12221904            | 12      |
| Caelo    | Elder flower, rubbed     | 12221903            | 1       |
| Caelo    | Elder flower, rubbed     | 10291212            | 1       |
| Caelo    | Elder flower, rubbed     | 12221910            | 4       |
| Caelo    | Elder flower, rubbed     | 13244601            | 4       |
| Caelo    | Elder flower, rubbed     | 13244602            | 4       |
| Caelo    | Elder flower, rubbed     | 13244604            | 1       |
| Caelo    | Elder flower, rubbed     | 13244606            | 1       |
| Caelo    | Elder flower, rubbed     | 13244610            | 1       |
| Caelo    | Elder flower, rubbed     | 14111317            | 1       |
| Caelo    | Elder flower, rubbed     | 15085301            | 1       |
| Caelo    | Elder flower, rubbed     | 15085314            | 1       |
| Caelo    | Elder flower, rubbed     | 25091207            | 1       |
| Caelo    | Elder flower, rubbed     | 12221907            | 4       |
| Caelo    | Elder root, cut          | 12345678            | 1       |
| Caelo    | Elecampane rhizome, cut  | 12113304            | 3       |
| Caelo    | Elecampane rhizome, cut  | 1211334             | 1       |
| Caelo    | Elecampane rhizome, cut  | 13152403            | 2       |
| Caelo    | Elecampane rhizome, cut  | 13152402            | 1       |
| Caelo    | Elecampane rhizome, cut  | 11374703            | 1       |
| Caelo    | Elecampane rhizome, cut  | 11374702            | 1       |
| Caelo    | Elecampane rhizome, cut  | 13152401            | 1       |
| Caelo    | Eleutherococcus, cut     | 10381818            | 2       |
| Caelo    | Eleutherococcus, cut     | 10381817            | 2       |
| Caelo    | Eleutherococcus, cut     | 12326707            | 1       |
| Caelo    | Eleutherococcus, cut     | 10381808            | 1       |

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| Supplier | Substance            | Batch               | Spectra |
|----------|----------------------|---------------------|---------|
| Caelo    | Eleutherococcus, cut | 10381812            | 2       |
| Caelo    | Eleutherococcus, cut | 12326701            | 2       |
| Caelo    | Eleutherococcus, cut | 10381814            | 2       |
| Caelo    | Eleutherococcus, cut | 12326703            | 1       |
| Caelo    | Elm bark, cut        | 12287902            | 4       |
| Caelo    | Elm bark, cut        | 10347204            | 1       |
| Caelo    | Elm bark, cut        | 10347203            | 1       |
| Caelo    | Equisetum stem, cut  |                     | 3       |
| Caelo    | Equisetum stem, cut  | 10375520            | 1       |
| Caelo    | Equisetum stem, cut  | 20111212            | 1       |
| Caelo    | Equisetum stem, cut  | 2658181             | 1       |
| Caelo    | Equisetum stem, cut  | 13344311            | 1       |
| Caelo    | Equisetum stem, cut  | 13344306            | 1       |
| Caelo    | Equisetum stem, cut  | 10375507            | 3       |
| Caelo    | Equisetum stem, cut  | 13344305            | 2       |
| Caelo    | Equisetum stem, cut  | 10328901            | 1       |
| Caelo    | Equisetum stem, cut  | 9101313             | 1       |
| Caelo    | Equisetum stem, cut  | 13344304            | 5       |
| Caelo    | Equisetum stem, cut  | 13344302            | 3       |
| Caelo    | Equisetum stem, cut  | 13159704            | 6       |
| Caelo    | Equisetum stem, cut  | 1288804             | 1       |
| Caelo    | Equisetum stem, cut  | 13091301            | 1       |
| Caelo    | Equisetum stem, cut  | 11021902            | 1       |
| Caelo    | Equisetum stem, cut  | 11021903            | 1       |
| Caelo    | Equisetum stem, cut  | 11076303            | 16      |
| Caelo    | Equisetum stem, cut  | 11076301            | 5       |
| Caelo    | Equisetum stem, cut  | 12288809            | 3       |
| Caelo    | Equisetum stem, cut  | 12288804            | 12      |
| Caelo    | Equisetum stem, cut  | 17011308            | 1       |
| Caelo    | Equisetum stem, cut  | 15015404            | 1       |
| Caelo    | Equisetum stem, cut  | 15015402            | 2       |
| Caelo    | Equisetum stem, cut  | 1359702             | 1       |
| Caelo    | Equisetum stem, cut  | 11021904            | 6       |
| Caelo    | Equisetum stem, cut  | 12288802            | 3       |
| Caelo    | Equisetum stem, cut  | 1228803             | 1       |
| Caelo    | Equisetum stem, cut  | 12268801            | 1       |
| Caelo    | Equisetum stem, cut  | 13350301            | 1       |
| Caelo    | Equisetum stem, cut  | 13344315            | 1       |
| Caelo    | Equisetum stem, cut  | 13344313            | 1       |
| Caelo    | Equisetum stem, cut  | 17101203            | 1       |
| Caelo    | Equisetum stem, cut  | 13350309            | 1       |
| Caelo    | Equisetum stem, cut  | 13344303            | 9       |
| Caelo    | Equisetum stem, cut  | 13159702            | 10      |
| Caelo    | Equisetum stem, cut  | 8051302             | 1       |
| Caelo    | Equisetum stem, cut  | 11076306            | 8       |
| Caelo    | Equisetum stem, cut  | 11076302            | 4       |
| Caelo    | Equisetum stem, cut  | 10328915            | 1       |
| Caelo    | Equisetum stem, cut  | 10375505            | 2       |
| Caelo    | Equisetum stem, cut  | 11021901            | 2       |
| Caelo    | Equisetum stem, cut  | 2613E-01642         | 1       |
| Caelo    | Equisetum stem, cut  | 13200201            | 1       |
| Caelo    | Equisetum stem, cut  | 11076307            | 3       |
| Caelo    | Equisetum stem, cut  | 12288808            | 10      |
| Caelo    | Equisetum stem, cut  | 12288801            | 15      |
| Caelo    | Equisetum stem, cut  | 13153702            | 1       |
| Caelo    | Equisetum stem, cut  | 1035515             | 1       |
| Caelo    | Equisetum stem, cut  | 13159702-3464312101 | 1       |
| Caelo    | Equisetum stem, cut  | 13159705            | 7       |
| Caelo    | Equisetum stem, cut  | 13159705-3387310190 | 1       |
| Caelo    | Equisetum stem, cut  | 13159706            | 6       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|--------------------------|---------------------|----------------|
| Caelo           | Equisetum stem, cut      | 12288803            | 19             |
| Caelo           | Equisetum stem, cut      | 8101201             | 1              |
| Caelo           | Equisetum stem, cut      | 12231401            | 14             |
| Caelo           | Equisetum stem, cut      | 13344309            | 5              |
| Caelo           | Equisetum stem, cut      | 30101305            | 1              |
| Caelo           | Equisetum stem, cut      | 282573              | 1              |
| Caelo           | Equisetum stem, cut      | 8041301             | 1              |
| Caelo           | Equisetum stem, cut      | 613M-01642          | 1              |
| Caelo           | Equisetum stem, cut      | 6081304             | 1              |
| Caelo           | Equisetum stem, cut      | 3091201             | 1              |
| Caelo           | Equisetum stem, cut      | 2011408             | 1              |
| Caelo           | Equisetum stem, cut      | 311042              | 1              |
| Caelo           | Eucalyptus leaf, cut     | 122250204           | 1              |
| Caelo           | Eucalyptus leaf, cut     | 11307706            | 1              |
| Caelo           | Eucalyptus leaf, cut     | 11307705            | 2              |
| Caelo           | Eucalyptus leaf, cut     | 11307703            | 3              |
| Caelo           | Eucalyptus leaf, cut     | 9346812             | 1              |
| Caelo           | Eucalyptus leaf, cut     | 9346807             | 1              |
| Caelo           | Eucalyptus leaf, cut     | 12225206            | 1              |
| Caelo           | Eucalyptus leaf, cut     | 9346811             | 3              |
| Caelo           | Eucalyptus leaf, cut     | 11307708            | 2              |
| Caelo           | Eucalyptus leaf, cut     | 12225202            | 1              |
| Caelo           | Eucalyptus leaf, cut     | 12225203            | 3              |
| Caelo           | Euphrasy herb, cut       | 13180005            | 2              |
| Caelo           | Euphrasy herb, cut       | 13180001            | 5              |
| Caelo           | Euphrasy herb, cut       | 13180002            | 4              |
| Caelo           | Euphrasy herb, cut       | 13180004            | 6              |
| Caelo           | Euphrasy herb, cut       | 12103202            | 10             |
| Caelo           | Euphrasy herb, cut       | 13180008            | 1              |
| Caelo           | Euphrasy herb, cut       | 14019102            | 2              |
| Caelo           | Euphrasy herb, cut       | 14019107            | 1              |
| Caelo           | Euphrasy herb, cut       | 29011302            | 1              |
| Caelo           | Euphrasy herb, cut       | 30101307            | 1              |
| Caelo           | Euphrasy herb, cut       | 1213202             | 1              |
| Caelo           | Euphrasy herb, cut       | 312052              | 1              |
| Caelo           | Euphrasy herb, cut       | 12103201            | 1              |
| Caelo           | Euphrasy herb, cut       | 11030812            | 4              |
| Caelo           | Euphrasy herb, cut       | 11030811            | 3              |
| Caelo           | Euphrasy herb, cut       | 11030810            | 1              |
| Caelo           | Euphrasy herb, cut       | 8011419             | 1              |
| Caelo           | Euphrasy herb, cut       | 7051302             | 1              |
| Caelo           | Euphrasy herb, cut       | 112211643           | 1              |
| Caelo           | Euphrasy herb, cut       | 9311411             | 1              |
| Caelo           | Euphrasy herb, cut       | 12103203            | 9              |
| Caelo           | European golden rod, ... | 12343102            | 1              |
| Caelo           | European golden rod, ... | 13386908            | 1              |
| Caelo           | European golden rod, ... | 12343103-3466312121 | 1              |
| Caelo           | Fenugreek                | 4912E-02803         | 1              |
| Caelo           | Fenugreek                | 13013805            | 3              |
| Caelo           | Fenugreek                | 13013802            | 2              |
| Caelo           | Fenugreek                | 12252603            | 2              |
| Caelo           | Fenugreek                | 11313204            | 4              |
| Caelo           | Fenugreek                | 1131206             | 1              |
| Caelo           | Fenugreek                | 10220701            | 1              |
| Caelo           | Fenugreek                | 13013801            | 2              |
| Caelo           | Fenugreek                | 12252601            | 2              |
| Caelo           | Fenugreek                | 11313205            | 1              |
| Caelo           | Fenugreek                | 13013803            | 7              |
| Caelo           | Fenugreek                | 11313203            | 3              |
| Caelo           | Fenugreek, powdered      | 15308703            | 2              |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Fenugreek, powdered      | 13398302            | 1       |
| Caelo    | Fenugreek, powdered      | 14057801            | 1       |
| Caelo    | Fenugreek, powdered      | 14057807            | 1       |
| Caelo    | Fenugreek, powdered      | 14377201            | 2       |
| Caelo    | Fenugreek, powdered      | 12149605            | 1       |
| Caelo    | Fenugreek, powdered      | 7264a110201         | 2       |
| Caelo    | Fenugreek, powdered      | 12149607            | 2       |
| Caelo    | Ferric (III) sulfate ... | 10354415            | 1       |
| Caelo    | Ferric (III) sulfate ... | 10354404            | 2       |
| Caelo    | Ferric (III) sulfate ... | 10354412            | 1       |
| Caelo    | Ferric (III) sulfate ... | 12175906            | 3       |
| Caelo    | Ferric (III) sulfate ... | 1512210007          | 2       |
| Caelo    | Ferric (III) sulfate ... | 12175908            | 1       |
| Caelo    | Feverfew herb, cut       | 12380204            | 1       |
| Caelo    | Feverfew herb, cut       | 12380203            | 6       |
| Caelo    | Flax weed herb, cut      | 14005303            | 1       |
| Caelo    | Flax weed herb, cut      | 14005305            | 3       |
| Caelo    | Flax weed herb, cut      | 13007505            | 2       |
| Caelo    | Flax weed herb, cut      | 14197204            | 1       |
| Caelo    | Flax weed herb, cut      | 16292801            | 1       |
| Caelo    | Flax weed herb, cut      | 11104505            | 1       |
| Caelo    | Flax weed herb, cut      | 11104507            | 11      |
| Caelo    | Flax weed herb, cut      | 13007507            | 7       |
| Caelo    | Flax weed herb, cut      | 13007502            | 3       |
| Caelo    | Frangula bark, cut       | 12186004            | 12      |
| Caelo    | Frangula bark, cut       | 10061301            | 1       |
| Caelo    | Frangula bark, cut       | eztetdt             | 1       |
| Caelo    | Frangula bark, cut       | 121860006           | 1       |
| Caelo    | Frangula bark, cut       | 12185901            | 9       |
| Caelo    | Frangula bark, cut       | 12186005            | 1       |
| Caelo    | Frangula bark, cut       | 11254001            | 3       |
| Caelo    | Frangula bark, cut       | 11340801            | 1       |
| Caelo    | Frangula bark, cut       | 13203008            | 2       |
| Caelo    | Frangula bark, cut       | 12186006            | 6       |
| Caelo    | Frangula bark, cut       | 14163102            | 1       |
| Caelo    | Frangula bark, cut       | 12186001            | 1       |
| Caelo    | Frangula bark, cut       | 12186002            | 16      |
| Caelo    | Frangula bark, cut       | 12186003            | 1       |
| Caelo    | Frangula bark, cut       | 1286003             | 1       |
| Caelo    | Frangula bark, cut       | 6011402             | 1       |
| Caelo    | Frankincense             | 13112801            | 5       |
| Caelo    | Frankincense             | 13112809            | 2       |
| Caelo    | Frankincense             | 15140809            | 1       |
| Caelo    | Frankincense             | 12120005            | 5       |
| Caelo    | Frankincense             | 12120012-3421310191 | 1       |
| Caelo    | Frankincense             | 13112803-3494411030 | 1       |
| Caelo    | Frankincense             | 15140805            | 2       |
| Caelo    | Frankincense             | 10349210            | 1       |
| Caelo    | Frankincense             | 15140804            | 1       |
| Caelo    | Frankincense             | 1210001             | 1       |
| Caelo    | Frankincense             | 1210005             | 1       |
| Caelo    | Frankincense             | 12120006            | 3       |
| Caelo    | Frankincense             | 14107803            | 2       |
| Caelo    | Frankincense             | 13112807            | 1       |
| Caelo    | Frankincense             | 100546              | 1       |
| Caelo    | Frankincense             | 13112803            | 1       |
| Caelo    | Frankincense             | 12120008            | 2       |
| Caelo    | Frankincense             | 12120007            | 1       |
| Caelo    | Frankincense             | 15140810            | 1       |
| Caelo    | Frankincense             | 4614M-02030         | 1       |

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| Supplier | Substance            | Batch               | Spectra |
|----------|----------------------|---------------------|---------|
| Caelo    | Fraxinella root, cut | 11314702            | 1       |
| Caelo    | Fumitory, cut        | 12103402            | 5       |
| Caelo    | Fumitory, cut        | 11101405            | 2       |
| Caelo    | Fumitory, cut        | 13202901            | 2       |
| Caelo    | Fumitory, cut        | 12103405            | 10      |
| Caelo    | Fumitory, cut        | 1110145             | 1       |
| Caelo    | Fumitory, cut        | 11101408            | 1       |
| Caelo    | Fumitory, cut        | 111011411           | 1       |
| Caelo    | Fumitory, cut        | 8312901             | 1       |
| Caelo    | Fumitory, cut        | 7111201             | 1       |
| Caelo    | Fumitory, cut        | 11101413            | 5       |
| Caelo    | Fumitory, cut        | 72878477            | 1       |
| Caelo    | Fumitory, cut        | 31081201            | 1       |
| Caelo    | Fumitory, cut        | 1320902             | 2       |
| Caelo    | Fumitory, cut        | 13202905            | 2       |
| Caelo    | Fumitory, cut        | 13202902            | 15      |
| Caelo    | Fumitory, cut        | 11101410            | 2       |
| Caelo    | Fumitory, cut        | 12103408            | 5       |
| Caelo    | Fumitory, cut        | 12103407            | 7       |
| Caelo    | Fumitory, cut        | 12103406            | 3       |
| Caelo    | Fumitory, cut        | 11101411            | 5       |
| Caelo    | Fumitory, cut        | 11101406            | 2       |
| Caelo    | Fumitory, cut        | 12103401            | 2       |
| Caelo    | Fumitory, cut        | 12103404            | 3       |
| Caelo    | Galangal root        | 12330306            | 2       |
| Caelo    | Galangal root        | 12125004            | 3       |
| Caelo    | Galangal root        | 13341105            | 1       |
| Caelo    | Galangal root        | 15128008            | 1       |
| Caelo    | Galangal root        | 1215004             | 1       |
| Caelo    | Galangal root        | 12330303            | 1       |
| Caelo    | Galangal root        | 12330305            | 2       |
| Caelo    | Galangal root        | 11375904            | 1       |
| Caelo    | Garden violet, cut   | 13232107            | 1       |
| Caelo    | Garden violet, cut   | 11124007            | 1       |
| Caelo    | Garden violet, cut   | 10291007            | 1       |
| Caelo    | Garden violet, cut   | 1021308             | 1       |
| Caelo    | Garden violet, cut   | 13038701            | 4       |
| Caelo    | Garden violet, cut   | 1303872             | 1       |
| Caelo    | Garden violet, cut   | 11124008            | 2       |
| Caelo    | Garden violet, cut   | 10011403            | 1       |
| Caelo    | Garden violet, cut   | 13038703            | 3       |
| Caelo    | Garden violet, cut   | 11124007-3284310662 | 1       |
| Caelo    | Gentian root, cut    | 12244607            | 1       |
| Caelo    | Gentian root, cut    | 10263413            | 1       |
| Caelo    | Gentian root, cut    | 6311B130305         | 3       |
| Caelo    | Gentian root, cut    | 3311i-02142         | 1       |
| Caelo    | Gentian root, cut    | 30011301            | 1       |
| Caelo    | Gentian root, cut    | 10263411            | 4       |
| Caelo    | Gentian root, cut    | 2913A-02142         | 1       |
| Caelo    | Gentian root, cut    | 10263406            | 1       |
| Caelo    | Gentian root, cut    | 10263404            | 2       |
| Caelo    | Gentian root, cut    | 10263403            | 1       |
| Caelo    | Gentian root, cut    | 10263401            | 1       |
| Caelo    | Gentian root, cut    | 19071304            | 1       |
| Caelo    | Gentian root, cut    | 13156102            | 1       |
| Caelo    | Gentian root, cut    | 12244608            | 1       |
| Caelo    | Gentian root, cut    | 1244603             | 1       |
| Caelo    | Gentian root, cut    | 10263405            | 1       |
| Caelo    | Gentian root, cut    | Int.Ch:313091       | 1       |
| Caelo    | Gentian root, cut    | Nachprüfung         | 1       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Gentian root, powdered   | 12007106            | 1       |
| Caelo    | Ginger, peeled           | 12164911-3368319002 | 1       |
| Caelo    | Ginger, peeled           | 11325712            | 1       |
| Caelo    | Ginger, peeled           | 13100604            | 1       |
| Caelo    | Ginger, peeled           | 13100605            | 4       |
| Caelo    | Ginger, peeled           | 11325706            | 1       |
| Caelo    | Ginger, peeled           | 13310602            | 2       |
| Caelo    | Ginger, peeled           | 19121201            | 1       |
| Caelo    | Ginger, peeled           | 13310604            | 3       |
| Caelo    | Ginger, peeled           | 13100602            | 2       |
| Caelo    | Ginger, peeled           | 11325715            | 2       |
| Caelo    | Ginger, peeled           | 11325716            | 1       |
| Caelo    | Ginger, peeled           | 11325719            | 3       |
| Caelo    | Ginger, peeled           | 11325703            | 2       |
| Caelo    | Ginger, peeled           | 11325713            | 1       |
| Caelo    | Ginger, peeled           | 12180604            | 1       |
| Caelo    | Ginger, peeled, powde... | 13092013B           | 1       |
| Caelo    | Ginger, peeled, powde... | 12164911            | 1       |
| Caelo    | Ginger, peeled, powde... | 12164901            | 1       |
| Caelo    | Ginkgo leaf, cut         | 15077407            | 1       |
| Caelo    | Ginkgo leaf, cut         | 13340904            | 1       |
| Caelo    | Ginkgo leaf, cut         | 12121703            | 1       |
| Caelo    | Ginkgo leaf, cut         | 12151703            | 1       |
| Caelo    | Ginkgo leaf, cut         | 13340901            | 1       |
| Caelo    | Ginkgo leaf, cut         | 13340906            | 1       |
| Caelo    | Ginkgo leaf, cut         | 13340907            | 1       |
| Caelo    | Ginkgo leaf, cut         | 10315510            | 1       |
| Caelo    | Ginkgo leaf, cut         | 12151707            | 2       |
| Caelo    | Ginkgo leaf, cut         | 12151709            | 2       |
| Caelo    | Ginkgo leaf, cut         | 1513E-02841         | 1       |
| Caelo    | Ginkgo leaf, cut         | nachprüfung         | 1       |
| Caelo    | Ginseng root             | 12080218            | 1       |
| Caelo    | Ginseng root             | 13341001            | 1       |
| Caelo    | Glucosamine sulfate 2... | 1122                | 1       |
| Caelo    | Goat's rue, cut          | 12343302            | 4       |
| Caelo    | Goat's rue, cut          | 12017907            | 3       |
| Caelo    | Goat's rue, cut          | 12017903            | 1       |
| Caelo    | Goat's rue, cut          | 11307901            | 1       |
| Caelo    | Goat's rue, cut          | 11175104            | 1       |
| Caelo    | Goat's rue, cut          | 6061203             | 1       |
| Caelo    | Goat's rue, cut          | 5122013e            | 1       |
| Caelo    | Goat's rue, cut          | 12017914            | 1       |
| Caelo    | Goat's rue, cut          | 11307903            | 2       |
| Caelo    | Goat's rue, cut          | 12017912            | 1       |
| Caelo    | Goat's rue, cut          | 12343303            | 7       |
| Caelo    | Goat's rue, cut          | 12017913            | 1       |
| Caelo    | Goat's rue, cut          | 12343308            | 2       |
| Caelo    | Goat's rue, cut          | 33131-01645         | 1       |
| Caelo    | Goat's rue, cut          | 12343305            | 3       |
| Caelo    | Ground ivy herb, cut     | 3411A-01651         | 1       |
| Caelo    | Ground ivy herb, cut     | 11052318            | 2       |
| Caelo    | Ground ivy herb, cut     | 11052311            | 1       |
| Caelo    | Ground ivy herb, cut     | 11052314            | 1       |
| Caelo    | Ground ivy herb, cut     | 11052315            | 1       |
| Caelo    | Ground ivy herb, cut     | 11374602            | 1       |
| Caelo    | Ground ivy herb, cut     | 11374606            | 1       |
| Caelo    | Ground ivy herb, cut     | 11374608            | 3       |
| Caelo    | Ground ivy herb, cut     | 11374609            | 1       |
| Caelo    | Ground ivy herb, cut     | 11374611            | 1       |
| Caelo    | Ground ivy herb, cut     | 11374615            | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>  | <b>Spectra</b> |
|-----------------|--------------------------|---------------|----------------|
| Caelo           | Ground ivy herb, cut     | 11374610      | 5              |
| Caelo           | Guaiacum wood, cut       | 4011M-01778   | 1              |
| Caelo           | Guaiacum wood, cut       | 11352012      | 1              |
| Caelo           | Guaiacum wood, cut       | 14008203      | 1              |
| Caelo           | Guaiacum wood, cut       | 10143014      | 1              |
| Caelo           | Guaiacum wood, cut       | 11352001      | 1              |
| Caelo           | Guaiacum wood, cut       | 11352008      | 1              |
| Caelo           | Guaiacum wood, cut       | nachprüfung   | 1              |
| Caelo           | Guaiacum wood, cut       | 8041401       | 1              |
| Caelo           | Hamamelis bark, cut      | 13123703      | 1              |
| Caelo           | Hamamelis bark, cut      | nachprüfung   | 1              |
| Caelo           | Hamamelis bark, cut      | 13123701      | 1              |
| Caelo           | Hamamelis bark, cut      | 12361301      | 1              |
| Caelo           | Hamamelis bark, cut      | 12361303      | 1              |
| Caelo           | Hamamelis leaf, cut      | 13269902      | 2              |
| Caelo           | Hamamelis leaf, cut      | 12164802      | 1              |
| Caelo           | Hamamelis leaf, cut      | 13269904      | 1              |
| Caelo           | Hamamelis leaf, cut      | 13269905      | 1              |
| Caelo           | Hamamelis leaf, cut      | 14356103      | 1              |
| Caelo           | Hamamelis leaf, cut      | 10102915      | 1              |
| Caelo           | Hamamelis leaf, cut      | 12165805      | 1              |
| Caelo           | Hamamelis leaf, cut      | 12164804      | 2              |
| Caelo           | Hawthorn flower          | 7121201       | 1              |
| Caelo           | Hawthorn flower          | 11068204      | 1              |
| Caelo           | Hawthorn flower          | 11068208      | 1              |
| Caelo           | Hawthorn flower          | 11068202      | 1              |
| Caelo           | Hawthorn flower          | 11068209      | 1              |
| Caelo           | Hawthorn flower          | 11068206      | 1              |
| Caelo           | Hawthorn flower          | 11068209      | 3              |
| Caelo           | Hawthorn flower          | 13010402      | 2              |
| Caelo           | Hawthorn flower          | 13010403      | 5              |
| Caelo           | Hawthorn flower          | 21051301      | 1              |
| Caelo           | Hawthorn flower          | 25101301      | 1              |
| Caelo           | Hawthorn flower          | 13010402      | 3              |
| Caelo           | Hawthorn flower          | 13253303      | 1              |
| Caelo           | Hawthorn flower          | 13253304      | 2              |
| Caelo           | Hawthorn flower          | 11068202      | 1              |
| Caelo           | Hawthorn fruit           | 12326306      | 1              |
| Caelo           | Hawthorn fruit           | 12326308      | 2              |
| Caelo           | Hawthorn fruit           | 12326304      | 1              |
| Caelo           | Hawthorn fruit           | 11278202      | 1              |
| Caelo           | Hawthorn fruit           | 13367203      | 1              |
| Caelo           | Hawthorn fruit           | 13101402      | 1              |
| Caelo           | Hawthorn fruit           | 12326307      | 2              |
| Caelo           | Hawthorn leaf with fl... | 12225104      | 12             |
| Caelo           | Hawthorn leaf with fl... | 12225103      | 5              |
| Caelo           | Hawthorn leaf with fl... | 11068206      | 1              |
| Caelo           | Hawthorn leaf with fl... | 10273415      | 1              |
| Caelo           | Hawthorn leaf with fl... | 10273514      | 1              |
| Caelo           | Hawthorn leaf with fl... | 10273512      | 2              |
| Caelo           | Hawthorn leaf with fl... | 10273511      | 1              |
| Caelo           | Hawthorn leaf with fl... | 12225107      | 6              |
| Caelo           | Hawthorn leaf with fl... | 2225104       | 1              |
| Caelo           | Hawthorn leaf with fl... | 109076        | 1              |
| Caelo           | Hawthorn leaf with fl... | 12225108      | 7              |
| Caelo           | Hawthorn leaf with fl... | 1221707       | 1              |
| Caelo           | Hawthorn leaf with fl... | 52467476      | 1              |
| Caelo           | Hawthorn leaf with fl... | 1222514       | 1              |
| Caelo           | Hawthorn leaf with fl... | IntCh: 313082 | 1              |
| Caelo           | Hawthorn leaf with fl... | 15188802      | 1              |

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| Supplier | Substance                  | Batch       | Spectra |
|----------|----------------------------|-------------|---------|
| Caelo    | Hawthorn leaf with fl. ... | 1518802     | 1       |
| Caelo    | Hawthorn leaf with fl. ... | 13276703    | 3       |
| Caelo    | Hawthorn leaf with fl. ... | 1412M-01485 | 1       |
| Caelo    | Hawthorn leaf with fl. ... | 1225107     | 1       |
| Caelo    | Hawthorn leaf with fl. ... | 12225207    | 1       |
| Caelo    | Hawthorn leaf with fl. ... | 16025802    | 1       |
| Caelo    | Hay flower                 | 13099205    | 1       |
| Caelo    | Hay flower                 | 13097304    | 1       |
| Caelo    | Hay flower                 | 11099915    | 1       |
| Caelo    | Hay flower                 | 12317110    | 2       |
| Caelo    | Hay flower                 | 11099916    | 1       |
| Caelo    | Hay flower                 | 12317101    | 10      |
| Caelo    | Hay flower                 | 12317102    | 2       |
| Caelo    | Hay flower                 | 14121301    | 1       |
| Caelo    | Hay flower                 | 11099910    | 1       |
| Caelo    | Hay flower                 | 13097302    | 7       |
| Caelo    | Hay flower                 | 13142402    | 1       |
| Caelo    | Hay flower                 | 12317107    | 12      |
| Caelo    | Hay flower                 | 12317104    | 10      |
| Caelo    | Hay flower                 | 11099909    | 3       |
| Caelo    | Hay flower                 | 12317108    | 3       |
| Caelo    | Hay flower                 | 3713E-01459 | 1       |
| Caelo    | Hay flower                 | 12371707    | 1       |
| Caelo    | Hay flower                 | 13097301    | 1       |
| Caelo    | Hay flower                 | 11099914    | 3       |
| Caelo    | Hay flower                 | 11099912    | 1       |
| Caelo    | Hay flower                 | 11099904    | 1       |
| Caelo    | Hay flower                 | 3713F-01459 | 1       |
| Caelo    | Hay flower                 | 11099902    | 1       |
| Caelo    | Hay flower                 | 12317103    | 1       |
| Caelo    | Hay flower                 | 25101202    | 1       |
| Caelo    | Heather flower, rubbed     | 13014206    | 1       |
| Caelo    | Heather flower, rubbed     | 10270516    | 1       |
| Caelo    | Heather flower, rubbed     | 13014204    | 5       |
| Caelo    | Heather, cut               | 13367502    | 1       |
| Caelo    | Heather, cut               | 11011209    | 2       |
| Caelo    | Heather, cut               | 11011208    | 1       |
| Caelo    | Heather, cut               | 9291512     | 1       |
| Caelo    | Heather, cut               | 11102901    | 1       |
| Caelo    | Heather, cut               | 28061201    | 1       |
| Caelo    | Heather, cut               | 11011207    | 1       |
| Caelo    | Heather, cut               | 19111203    | 1       |
| Caelo    | Heavy alkaline bismut. ... | 11052805    | 1       |
| Caelo    | Heavy alkaline bismut. ... | 10013208    | 1       |
| Caelo    | Heavy alkaline bismut. ... | 10F09-N13   | 1       |
| Caelo    | Heavy alkaline bismut. ... | 12C08-N06   | 3       |
| Caelo    | Heavy alkaline bismut. ... | 12146902    | 1       |
| Caelo    | Heavy alkaline bismut. ... | 3081205     | 1       |
| Caelo    | Heavy alkaline bismut. ... | 12146903    | 7       |
| Caelo    | Heavy alkaline bismut. ... | 12146909    | 4       |
| Caelo    | Heavy alkaline bismut. ... | 12146911    | 4       |
| Caelo    | Heavy alkaline bismut. ... | 12146913    | 3       |
| Caelo    | Heavy alkaline bismut. ... | 11052812    | 2       |
| Caelo    | Heavy alkaline bismut. ... | 11052817    | 1       |
| Caelo    | Heavy alkaline bismut. ... | 11052809    | 1       |
| Caelo    | Heavy alkaline bismut. ... | 4513M-01186 | 1       |
| Caelo    | Heavy alkaline bismut. ... | M468105     | 1       |
| Caelo    | Heavy alkaline bismut. ... | 10013213    | 1       |
| Caelo    | Heavy, basic magnesiu. ... | 12135404    | 1       |
| Caelo    | Heavy, basic magnesiu. ... | 7011404     | 1       |

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| Supplier | Substance               | Batch               | Spectra |
|----------|-------------------------|---------------------|---------|
| Caelo    | Heavy, basic magnesi... | 2091303             | 1       |
| Caelo    | Heavy, basic magnesi... | 12135401            | 1       |
| Caelo    | Heavy, basic magnesi... | 13123505            | 1       |
| Caelo    | Heavy, basic magnesi... | 13123504            | 2       |
| Caelo    | Heavy, basic magnesi... | 13123502            | 1       |
| Caelo    | Henna powder            | 12267311            | 1       |
| Caelo    | Henna powder            | 12122310            | 3       |
| Caelo    | Henna powder            | 13262803            | 2       |
| Caelo    | Hop strobile            | 12008312            | 1       |
| Caelo    | Hop strobile            | 13123806            | 1       |
| Caelo    | Hop strobile            | 13220502            | 1       |
| Caelo    | Hop strobile            | 13187602            | 1       |
| Caelo    | Hop strobile            | 5021306             | 1       |
| Caelo    | Hop strobile            | 1451b120817         | 2       |
| Caelo    | Hop strobile            | 13123804-3563412081 | 1       |
| Caelo    | Hop strobile            | 14068001            | 1       |
| Caelo    | Hop strobile            | 13123808            | 2       |
| Caelo    | Hop strobile            | 13123807            | 1       |
| Caelo    | Hop strobile            | 13123804            | 3       |
| Caelo    | Hop strobile            | 15061211            | 1       |
| Caelo    | Hop strobile            | 120008312           | 1       |
| Caelo    | Hop strobile            | 4111304             | 1       |
| Caelo    | Hop strobile            | 12006305            | 1       |
| Caelo    | Hop strobile            | 12008306            | 1       |
| Caelo    | Hop strobile            | 13123802            | 4       |
| Caelo    | Hop strobile            | 12380101            | 1       |
| Caelo    | Hop strobile            | 12221805            | 6       |
| Caelo    | Hop strobile            | 12221804            | 1       |
| Caelo    | Hop strobile            | 12221802            | 2       |
| Caelo    | Hop strobile            | 13123803-3505411011 | 1       |
| Caelo    | Hop strobile            | 13123803            | 8       |
| Caelo    | Hop strobile            | 13123802            | 10      |
| Caelo    | Hop strobile            | 12221807            | 1       |
| Caelo    | Hop strobile            | 12008317            | 1       |
| Caelo    | Hop strobile            | 13123803            | 1       |
| Caelo    | Hop strobile            | 12008313            | 2       |
| Caelo    | Hop strobile            | 12008309            | 5       |
| Caelo    | Hop strobile            | 12380103            | 1       |
| Caelo    | Hop strobile            | 10240410            | 1       |
| Caelo    | Hop strobile            | 131223805           | 1       |
| Caelo    | Hop strobile            | 10240308            | 1       |
| Caelo    | Hop strobile            | 10036008            | 1       |
| Caelo    | Hop strobile            | 12008310            | 3       |
| Caelo    | Hop strobile            | 12008303            | 1       |
| Caelo    | Hop strobile            | 4756769             | 1       |
| Caelo    | Hop strobile            | 12008315            | 1       |
| Caelo    | Hop strobile            | 12008311            | 1       |
| Caelo    | Hop strobile            | 12008307            | 3       |
| Caelo    | Hop strobile            | 12008302            | 3       |
| Caelo    | Hop strobile            | 12008310            | 4       |
| Caelo    | Hop strobile            | 12380101            | 8       |
| Caelo    | Hop strobile            | 4212M-023337        | 1       |
| Caelo    | Hop strobile            | 30121301            | 1       |
| Caelo    | Hop strobile            | 12008317            | 7       |
| Caelo    | Hop strobile            | 14068007            | 1       |
| Caelo    | Hop strobile            | 12008305            | 4       |
| Caelo    | Hop strobile            | 12092001            | 5       |
| Caelo    | Hop strobile            | 1451B120202         | 8       |
| Caelo    | Hop strobile            | 12380102            | 1       |
| Caelo    | Hop strobile            | 6091303             | 1       |

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| Supplier | Substance                | Batch       | Spectra |
|----------|--------------------------|-------------|---------|
| Caelo    | Hop strobile             | 10240320    | 1       |
| Caelo    | Horse chestnut leaf, ... | 11063503    | 4       |
| Caelo    | Horse chestnut leaf, ... | 11063504    | 2       |
| Caelo    | Horse chestnut leaf, ... | 13126501    | 1       |
| Caelo    | Hydromorphone hydroch... | 15393605    | 1       |
| Caelo    | Hydromorphone hydroch... | 16123805    | 1       |
| Caelo    | Hyssop herb, cut         | 11374303    | 2       |
| Caelo    | Hyssop herb, cut         | 13143902    | 1       |
| Caelo    | Hyssop herb, cut         | 11374304    | 1       |
| Caelo    | Iceland moss, cut        | 13350807    | 5       |
| Caelo    | Iceland moss, cut        | 11101601    | 1       |
| Caelo    | Iceland moss, cut        | 12198102    | 1       |
| Caelo    | Iceland moss, cut        | 12382806    | 1       |
| Caelo    | Iceland moss, cut        | 11101502    | 1       |
| Caelo    | Iceland moss, cut        | 14304409    | 5       |
| Caelo    | Iceland moss, cut        | 14304403    | 2       |
| Caelo    | Iceland moss, cut        | 12187101    | 2       |
| Caelo    | Iceland moss, cut        | 4912E-01774 | 2       |
| Caelo    | Iceland moss, cut        | nachprüfung | 1       |
| Caelo    | Iceland moss, cut        | 12187103    | 1       |
| Caelo    | Iceland moss, cut        | 1218702     | 1       |
| Caelo    | Iceland moss, cut        | 14304401    | 1       |
| Caelo    | Iceland moss, cut        | 11101606    | 2       |
| Caelo    | Iceland moss, cut        | 11053911    | 1       |
| Caelo    | Iceland moss, cut        | 12187107    | 1       |
| Caelo    | Iceland moss, cut        | 1287102     | 1       |
| Caelo    | Iceland moss, cut        | 13350803    | 4       |
| Caelo    | Iceland moss, cut        | 11101607    | 12      |
| Caelo    | Iceland moss, cut        | 9052804     | 2       |
| Caelo    | Iceland moss, cut        | 12187106    | 3       |
| Caelo    | Iceland moss, cut        | 12197002    | 1       |
| Caelo    | Iceland moss, cut        | 11101604    | 1       |
| Caelo    | Iceland moss, cut        | 12187002    | 3       |
| Caelo    | Iceland moss, cut        | 12187104    | 8       |
| Caelo    | Iceland moss, cut        | 12187109    | 5       |
| Caelo    | Iceland moss, cut        | 11053916    | 1       |
| Caelo    | Iceland moss, cut        | 2811e-01774 | 1       |
| Caelo    | Iceland moss, cut        | 12187102    | 19      |
| Caelo    | Iceland moss, cut        | 14304402    | 1       |
| Caelo    | Iceland moss, cut        | 15297605    | 1       |
| Caelo    | Ispaghula seed           | 1227506     | 2       |
| Caelo    | Ispaghula seed           | 19061308    | 1       |
| Caelo    | Ispaghula seed           | 12276501    | 2       |
| Caelo    | Ispaghula seed           | 12276511    | 1       |
| Caelo    | Ispaghula seed           | 11061405    | 1       |
| Caelo    | Ispaghula seed           | 30101303    | 1       |
| Caelo    | Ispaghula seed           | 10011303    | 1       |
| Caelo    | Ispaghula seed           | 11185803    | 1       |
| Caelo    | Ispaghula seed           | 23011505    | 1       |
| Caelo    | Ispaghula seed           | 15249320    | 1       |
| Caelo    | Ispaghula seed           | 11185811    | 2       |
| Caelo    | Ispaghula seed           | 15249319    | 2       |
| Caelo    | Ispaghula seed           | 15121902    | 3       |
| Caelo    | Ispaghula seed           | 15249315    | 1       |
| Caelo    | Ispaghula seed           | 15249313    | 1       |
| Caelo    | Ispaghula seed           | 15249308    | 3       |
| Caelo    | Ispaghula seed           | 14031408    | 1       |
| Caelo    | Ispaghula seed           | 12252706    | 1       |
| Caelo    | Ispaghula seed           | 12252709    | 1       |
| Caelo    | Ispaghula seed           | 4121201     | 1       |

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| <b>Supplier</b> | <b>Substance</b> | <b>Batch</b> | <b>Spectra</b> |
|-----------------|------------------|--------------|----------------|
| Caelo           | Ispaghula seed   | 15081503     | 1              |
| Caelo           | Ispaghula seed   | 14246603     | 2              |
| Caelo           | Ispaghula seed   | 3912Q-03369  | 1              |
| Caelo           | Ispaghula seed   | 29061510     | 1              |
| Caelo           | Ispaghula seed   | 18071301     | 1              |
| Caelo           | Ispaghula seed   | 16121302     | 1              |
| Caelo           | Ispaghula seed   | 4114001      | 1              |
| Caelo           | Ispaghula seed   | 3051303      | 1              |
| Caelo           | Ispaghula seed   | 26011401     | 1              |
| Caelo           | Ispaghula seed   | 3051302      | 1              |
| Caelo           | Ispaghula seed   | 9011302      | 1              |
| Caelo           | Ispaghula seed   | 30101302     | 1              |
| Caelo           | Ispaghula seed   | 4121202      | 1              |
| Caelo           | Ispaghula seed   | 413E-03369   | 1              |
| Caelo           | Ispaghula seed   | 5091319      | 1              |
| Caelo           | Ivy leaf, cut    | 20111211     | 1              |
| Caelo           | Ivy leaf, cut    | 23121305     | 1              |
| Caelo           | Ivy leaf, cut    | 23121303     | 1              |
| Caelo           | Ivy leaf, cut    | nachprüfung  | 2              |
| Caelo           | Ivy leaf, cut    | 15101203     | 1              |
| Caelo           | Ivy leaf, cut    | 1021306      | 1              |
| Caelo           | Ivy leaf, cut    | 12225605     | 5              |
| Caelo           | Ivy leaf, cut    | 2031301      | 1              |
| Caelo           | Ivy leaf, cut    | 4011301      | 1              |
| Caelo           | Ivy leaf, cut    | 410E-0149    | 1              |
| Caelo           | Ivy leaf, cut    | 12225603     | 3              |
| Caelo           | Ivy leaf, cut    | 8061205      | 1              |
| Caelo           | Ivy leaf, cut    | 12225602     | 2              |
| Caelo           | Ivy leaf, cut    | 11229505     | 5              |
| Caelo           | Ivy leaf, cut    | 11101205     | 1              |
| Caelo           | Ivy leaf, cut    | 10011401     | 1              |
| Caelo           | Ivy leaf, cut    | 11041303     | 1              |
| Caelo           | Ivy leaf, cut    | 11041304     | 1              |
| Caelo           | Ivy leaf, cut    | 25021305     | 1              |
| Caelo           | Ivy leaf, cut    | 15121205     | 1              |
| Caelo           | Ivy leaf, cut    | 27111301     | 1              |
| Caelo           | Jasmine flower   | 12143203     | 4              |
| Caelo           | Java tea, cut    | 1121905      | 1              |
| Caelo           | Java tea, cut    | 12225702     | 1              |
| Caelo           | Java tea, cut    | 12225704     | 5              |
| Caelo           | Java tea, cut    | 11212901     | 2              |
| Caelo           | Java tea, cut    | 13258801     | 2              |
| Caelo           | Java tea, cut    | 23051203     | 1              |
| Caelo           | Java tea, cut    | 28101305     | 1              |
| Caelo           | Java tea, cut    | 31081207     | 1              |
| Caelo           | Java tea, cut    | 31121203     | 1              |
| Caelo           | Java tea, cut    | 2221B121112  | 17             |
| Caelo           | Java tea, cut    | 11212905     | 2              |
| Caelo           | Java tea, cut    | 2221A110825  | 3              |
| Caelo           | Java tea, cut    | 13258802     | 2              |
| Caelo           | Java tea, cut    | 21061304     | 1              |
| Caelo           | Java tea, cut    | 20111207     | 1              |
| Caelo           | Java tea, cut    | 13258803     | 1              |
| Caelo           | Java tea, cut    | 13258804     | 3              |
| Caelo           | Java tea, cut    | 14121-01507  | 1              |
| Caelo           | Java tea, cut    | 11212904     | 1              |
| Caelo           | Juniper          | 12028601     | 1              |
| Caelo           | Juniper          | 12113701     | 1              |
| Caelo           | Juniper          | 2890a101201  | 3              |
| Caelo           | Juniper          | 12330504     | 1              |

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| Supplier | Substance                  | Batch       | Spectra |
|----------|----------------------------|-------------|---------|
| Caelo    | Juniper                    | 12330501    | 1       |
| Caelo    | Juniper                    | 12028604    | 1       |
| Caelo    | Juniper                    | 12028608    | 1       |
| Caelo    | Juniper, pounded           | 13367302    | 1       |
| Caelo    | Juniper, pounded           | 13031302    | 1       |
| Caelo    | Kaolin, heavy              | 82043269    | 1       |
| Caelo    | Kaolin, heavy              | 13041835    | 1       |
| Caelo    | Kaolin, heavy              | 10176530    | 1       |
| Caelo    | Kaolin, heavy              | 11350125    | 6       |
| Caelo    | Kaolin, heavy              | 11350107    | 5       |
| Caelo    | Kaolin, heavy              | 13041834    | 1       |
| Caelo    | Kaolin, heavy              | 13041835    | 3       |
| Caelo    | Kaolin, heavy              | 63033516    | 1       |
| Caelo    | Kaolin, heavy              | 13041803    | 2       |
| Caelo    | Kaolin, heavy              | 11350124    | 4       |
| Caelo    | Kaolin, heavy              | 11350106    | 2       |
| Caelo    | Kaolin, heavy              | 11041610    | 1       |
| Caelo    | Kaolin, heavy              | 11350115    | 1       |
| Caelo    | Kaolin, heavy              | 11350107    | 1       |
| Caelo    | Kaolin, heavy              | 11041623    | 2       |
| Caelo    | Kaolin, heavy              | 10176518    | 1       |
| Caelo    | Kelp, cut                  | 1313E-01558 | 1       |
| Caelo    | Kelp, cut                  | 14071502    | 1       |
| Caelo    | Kelp, cut                  | 11351109    | 1       |
| Caelo    | Kelp, cut                  | 280172      | 4       |
| Caelo    | Kelp, cut                  | 11351111    | 1       |
| Caelo    | Kelp, cut                  | 11352209    | 1       |
| Caelo    | Kidney vetch, coarsel. ... | 13104301    | 2       |
| Caelo    | Knotgrass, cut             | 8111202     | 1       |
| Caelo    | Knotgrass, cut             | 11369301    | 1       |
| Caelo    | Knotgrass, cut             | 7102427     | 1       |
| Caelo    | Knotgrass, cut             | 12295702    | 3       |
| Caelo    | Knotgrass, cut             | 12295704    | 7       |
| Caelo    | Knotgrass, cut             | 12368903    | 1       |
| Caelo    | Knotgrass, cut             | 12368904    | 1       |
| Caelo    | Knotgrass, cut             | 14079304    | 1       |
| Caelo    | Knotgrass, cut             | 4301A100126 | 2       |
| Caelo    | Knotgrass, cut             | 12368902    | 7       |
| Caelo    | Knotgrass, cut             | 4312M-01674 | 1       |
| Caelo    | Ladys bedstraw herb,...    | 24101201    | 1       |
| Caelo    | Ladys bedstraw herb,...    | 15029906    | 1       |
| Caelo    | Ladys bedstraw herb,...    | 12369001    | 3       |
| Caelo    | Ladys bedstraw herb,...    | 12369007    | 4       |
| Caelo    | Ladys bedstraw herb,...    | 12369006    | 6       |
| Caelo    | Ladys bedstraw herb,...    | 12369002    | 3       |
| Caelo    | Ladys bedstraw herb,...    | 10375702    | 1       |
| Caelo    | Ladys bedstraw herb,...    | 11265106    | 1       |
| Caelo    | Ladys bedstraw herb,...    | 11265105    | 1       |
| Caelo    | Ladys bedstraw herb,...    | 11265104    | 5       |
| Caelo    | Ladys bedstraw herb,...    | 11265103    | 5       |
| Caelo    | Ladys bedstraw herb,...    | 14019202    | 1       |
| Caelo    | Ladys bedstraw herb,...    | 11265101    | 1       |
| Caelo    | Ladys bedstraw herb,...    | 11265102    | 11      |
| Caelo    | Ladys bedstraw herb,...    | 10375707    | 3       |
| Caelo    | Ladys bedstraw herb,...    | 7011301     | 1       |
| Caelo    | Ladys bedstraw herb,...    | 10375703    | 3       |
| Caelo    | Ladys bedstraw herb,...    | 2401311647  | 1       |
| Caelo    | Ladys bedstraw herb,...    | 204211647   | 1       |
| Caelo    | Ladys bedstraw herb,...    | 22041303    | 1       |
| Caelo    | Ladys bedstraw herb,...    | 10375708    | 1       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Lapacho wood, cut        | 13298308            | 1       |
| Caelo    | Lapacho wood, cut        | 11154506            | 1       |
| Caelo    | Lapacho wood, cut        | 12239305            | 8       |
| Caelo    | Lapacho wood, cut        | 2x11154506          | 1       |
| Caelo    | Lapacho wood, cut        | 12239303            | 2       |
| Caelo    | Lapacho wood, cut        | 13298305            | 1       |
| Caelo    | Lapacho wood, cut        | 19061301            | 1       |
| Caelo    | Large waybread herb, ... | 10349603            | 2       |
| Caelo    | Large waybread herb, ... | 9311208             | 1       |
| Caelo    | Large waybread herb, ... | 12374106            | 1       |
| Caelo    | Large waybread herb, ... | 10349610            | 2       |
| Caelo    | Large waybread herb, ... | 14125907            | 1       |
| Caelo    | Large waybread herb, ... | 13232404            | 1       |
| Caelo    | Large waybread herb, ... | 10349614            | 1       |
| Caelo    | Large waybread herb, ... | 123741004           | 1       |
| Caelo    | Large waybread herb, ... | 13232401            | 2       |
| Caelo    | Large waybread herb, ... | 12374101            | 4       |
| Caelo    | Large waybread herb, ... | 10349605            | 2       |
| Caelo    | Laurel leaf              | 12299106            | 3       |
| Caelo    | Lavender flower          | 11327905            | 2       |
| Caelo    | Lavender flower          | 11305403            | 1       |
| Caelo    | Lavender flower          | 13336008            | 1       |
| Caelo    | Lavender flower          | 11327903            | 13      |
| Caelo    | Lavender flower          | 13159602            | 1       |
| Caelo    | Lavender flower          | 11054104            | 2       |
| Caelo    | Lavender flower          | 13159601            | 1       |
| Caelo    | Lavender flower          | 12088006            | 4       |
| Caelo    | Lavender flower          | 13185001-3415310152 | 1       |
| Caelo    | Lavender flower          | 13185001            | 27      |
| Caelo    | Lavender flower          | 12088005            | 4       |
| Caelo    | Lavender flower          | 13185003            | 11      |
| Caelo    | Lavender flower          | 1318501             | 1       |
| Caelo    | Lavender flower          | 6091304             | 1       |
| Caelo    | Lavender flower          | 13185006            | 1       |
| Caelo    | Lavender flower          | 12031302            | 1       |
| Caelo    | Lavender flower          | 12088003            | 14      |
| Caelo    | Lavender flower          | 12088002            | 4       |
| Caelo    | Lavender flower          | 27091202            | 1       |
| Caelo    | Lavender flower          | 13185001-3389311070 | 1       |
| Caelo    | Lavender flower          | 15061201            | 1       |
| Caelo    | Lavender flower          | 15061209            | 1       |
| Caelo    | Lavender flower          | 12088001            | 1       |
| Caelo    | Lavender flower          | 313A-01462          | 1       |
| Caelo    | Lavender flower          | 13185002            | 1       |
| Caelo    | Lavender flower          | 11054107            | 1       |
| Caelo    | Lavender flower          | 11054106            | 4       |
| Caelo    | Lavender flower          | 19071303            | 1       |
| Caelo    | Lavender flower          | 13387204            | 1       |
| Caelo    | Lemon grass, cut         | 13149703            | 1       |
| Caelo    | Lemon grass, cut         | 11301509            | 4       |
| Caelo    | Lemon grass, cut         | 13149701            | 5       |
| Caelo    | Lemon grass, cut         | 11301503            | 1       |
| Caelo    | Lemon grass, cut         | 13341301            | 1       |
| Caelo    | Lemon grass, cut         | 11301501            | 1       |
| Caelo    | Lemon peel, cut          | 12217401            | 1       |
| Caelo    | Lemon peel, cut          | 12217404            | 1       |
| Caelo    | Lemon peel, cut          | 12217402            | 2       |
| Caelo    | Lemon verbena leaf, cut  | 10018208            | 1       |
| Caelo    | Lemon verbena leaf, cut  | 13037702            | 1       |
| Caelo    | Lemon verbena leaf, cut  | 12137507            | 4       |

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| Supplier | Substance               | Batch               | Spectra |
|----------|-------------------------|---------------------|---------|
| Caelo    | Lemon verbena leaf, cut | 12137505            | 2       |
| Caelo    | Lime flower, cut        | 268709              | 4       |
| Caelo    | Lime flower, cut        | 10273606            | 1       |
| Caelo    | Lime flower, cut        | 11086305            | 8       |
| Caelo    | Lime flower, cut        | 13337403-348012102  | 1       |
| Caelo    | Lime flower, cut        | 12170702-3355319071 | 1       |
| Caelo    | Lime flower, cut        | Int.Ch:210140       | 1       |
| Caelo    | Lime flower, cut        | 9206604             | 1       |
| Caelo    | Lime flower, cut        | 3212M-01474         | 1       |
| Caelo    | Lime flower, cut        | 12170701            | 1       |
| Caelo    | Lime flower, cut        | 11086301            | 1       |
| Caelo    | Lime flower, cut        | 11086307            | 3       |
| Caelo    | Lime flower, cut        | 13337403            | 5       |
| Caelo    | Lime flower, cut        | 15068302            | 1       |
| Caelo    | Lime flower, cut        | 1210702             | 1       |
| Caelo    | Lime flower, cut        | 13101708            | 2       |
| Caelo    | Lime flower, cut        | 15111301            | 1       |
| Caelo    | Lime flower, cut        | 11086306            | 1       |
| Caelo    | Lime flower, cut        | 25091206            | 1       |
| Caelo    | Lime flower, cut        | 272958              | 7       |
| Caelo    | Lime flower, cut        | 28031302            | 1       |
| Caelo    | Lime flower, cut        | 13101701            | 6       |
| Caelo    | Lime flower, cut        | 12170703            | 2       |
| Caelo    | Lime flower, cut        | 13101702            | 9       |
| Caelo    | Lime flower, cut        | 1913E-01474         | 1       |
| Caelo    | Lime leaf, cut          | 1611A121120         | 1       |
| Caelo    | Linseed                 | 11177305            | 1       |
| Caelo    | Linseed                 | 1326703             | 2       |
| Caelo    | Linseed                 | 13262704            | 2       |
| Caelo    | Linseed                 | 13262703            | 3       |
| Caelo    | Linseed                 | 13140305            | 1       |
| Caelo    | Linseed                 | 3213A-02240         | 1       |
| Caelo    | Linseed                 | 12092102            | 4       |
| Caelo    | Linseed                 | 12321604            | 3       |
| Caelo    | Linseed                 | 13121207            | 1       |
| Caelo    | Linseed                 | 11199003            | 1       |
| Caelo    | Linseed                 | 11199006            | 2       |
| Caelo    | Linseed                 | 11365508            | 1       |
| Caelo    | Linseed                 | 12382006            | 3       |
| Caelo    | Linseed                 | 13296705            | 5       |
| Caelo    | Linseed                 | 4713U02240          | 1       |
| Caelo    | Linseed                 | 13296707            | 1       |
| Caelo    | Linseed                 | 12321606            | 2       |
| Caelo    | Linseed                 | 15006601            | 1       |
| Caelo    | Linseed                 | 12382002            | 2       |
| Caelo    | Linseed                 | 18111302            | 1       |
| Caelo    | Linseed                 | 16040001            | 1       |
| Caelo    | Linseed                 | 16011405            | 1       |
| Caelo    | Linseed                 | 12321607            | 1       |
| Caelo    | Linseed                 | 11365507            | 4       |
| Caelo    | Linseed                 | 11365504            | 2       |
| Caelo    | Linseed                 | 28051303            | 1       |
| Caelo    | Linseed                 | 15321902            | 1       |
| Caelo    | Linseed                 | 15006607            | 1       |
| Caelo    | Linseed                 | 13412804            | 1       |
| Caelo    | Linseed                 | 14262906            | 2       |
| Caelo    | Linseed                 | 15006005            | 1       |
| Caelo    | Linseed                 | 15006605            | 1       |
| Caelo    | Linseed                 | 15006602            | 2       |
| Caelo    | Linseed                 | 15061201            | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b> | <b>Spectra</b> |
|-----------------|--------------------------|--------------|----------------|
| Caelo           | Linseed                  | 28051403     | 1              |
| Caelo           | Linseed                  | 16011403     | 1              |
| Caelo           | Linseed                  | 1232006      | 1              |
| Caelo           | Linseed                  | 12382004     | 3              |
| Caelo           | Linseed                  | 12092103     | 3              |
| Caelo           | Linseed                  | 12092104     | 2              |
| Caelo           | Linseed                  | 12186901     | 2              |
| Caelo           | Linseed                  | 12321602     | 4              |
| Caelo           | Linseed                  | 7370A131104  | 2              |
| Caelo           | Linseed                  | 12321601     | 2              |
| Caelo           | Linseed                  | 15053702     | 1              |
| Caelo           | Linseed                  | 13296702     | 4              |
| Caelo           | Linseed                  | 13262702     | 2              |
| Caelo           | Liquorice root, peeled   | 1135904      | 1              |
| Caelo           | Liquorice root, peeled   | 12227112     | 1              |
| Caelo           | Liquorice root, peeled   | 12227101     | 1              |
| Caelo           | Liquorice root, peeled   | 13104503     | 3              |
| Caelo           | Liquorice root, peeled   | 13194101     | 7              |
| Caelo           | Liquorice root, peeled   | 1351911      | 1              |
| Caelo           | Liquorice root, peeled   | 18121302     | 1              |
| Caelo           | Liquorice root, peeled   | 10011301     | 1              |
| Caelo           | Liquorice root, peeled   | 24131-02151  | 1              |
| Caelo           | Liquorice root, peeled   | 6381A-121126 | 1              |
| Caelo           | Liquorice root, peeled   | 638a120806   | 1              |
| Caelo           | Liquorice root, peeled   | 11351903     | 1              |
| Caelo           | Liquorice root, peeled   | 11351911     | 5              |
| Caelo           | Liquorice root, peeled   | 277004       | 1              |
| Caelo           | Liquorice root, peeled   | 11351905     | 5              |
| Caelo           | Liquorice root, peeled   | 11351906     | 5              |
| Caelo           | Liquorice root, peeled   | 11351913     | 2              |
| Caelo           | Liquorice root, peeled   | 11351910     | 3              |
| Caelo           | Liquorice root, peeled   | 11351904     | 1              |
| Caelo           | Liquorice root, peeled   | 13104504     | 5              |
| Caelo           | Liquorice root, natur... | 10110912     | 1              |
| Caelo           | Liquorice root, natur... | 281844       | 2              |
| Caelo           | Liquorice root, natur... | 12267103     | 1              |
| Caelo           | Liquorice root, natur... | 12267104     | 3              |
| Caelo           | Liquorice root, natur... |              | 1              |
| Caelo           | Liquorice root, natur... | 13037904     | 1              |
| Caelo           | Liquorice root, natur... | 13037902     | 1              |
| Caelo           | Lovage root, cut         | 11181609     | 3              |
| Caelo           | Lovage root, cut         | 12169009     | 1              |
| Caelo           | Lovage root, cut         | 12169010     | 2              |
| Caelo           | Lovage root, cut         | 4312M-02150  | 1              |
| Caelo           | Lovage root, cut         | 107063       | 1              |
| Caelo           | Lovage root, cut         | 13385005     | 1              |
| Caelo           | Lovage root, cut         | 10249313     | 1              |
| Caelo           | Lovage root, cut         | 11181611     | 3              |
| Caelo           | Lovage root, cut         | 1181608      | 1              |
| Caelo           | Lovage root, cut         | 12169008     | 4              |
| Caelo           | Lovage root, cut         | 12169002     | 2              |
| Caelo           | Lovage root, cut         | 12169012     | 1              |
| Caelo           | Lovage root, cut         | 12169003     | 1              |
| Caelo           | Lovage root, cut         | 12189001     | 1              |
| Caelo           | Lovage root, cut         | 12189002     | 1              |
| Caelo           | Lovage root, cut         | 12169006     | 3              |
| Caelo           | Lungwort herb, cut       | 11134203     | 14             |
| Caelo           | Lungwort herb, cut       | 13355801     | 2              |
| Caelo           | Lungwort herb, cut       | 11134205     | 3              |
| Caelo           | Lungwort herb, cut       | 4331b111205  | 1              |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Lungwort herb, cut       | 11134201            | 1       |
| Caelo    | Lungwort herb, cut       | 11021709            | 2       |
| Caelo    | Lungwort herb, cut       | 713M-01675          | 1       |
| Caelo    | Lungwort herb, cut       | 11021707            | 2       |
| Caelo    | Lungwort herb, cut       | 13029306            | 2       |
| Caelo    | Lungwort herb, cut       | 11134202            | 3       |
| Caelo    | Lungwort herb, cut       | 13029302            | 26      |
| Caelo    | Lungwort herb, cut       | 13029304            | 6       |
| Caelo    | Lycopodium herb, cut     | 11255001            | 2       |
| Caelo    | Lycopodium herb, cut     | 11255005            | 5       |
| Caelo    | Lycopodium herb, cut     | 11255003            | 2       |
| Caelo    | Lycopodium herb, cut     | 11255008            | 16      |
| Caelo    | Lycopodium herb, cut     | 13101501            | 1       |
| Caelo    | Lycopodium herb, cut     | 11255009            | 5       |
| Caelo    | Lycopodium herb, cut     | 11255010            | 1       |
| Caelo    | Lycopodium herb, cut     | 11255011            | 9       |
| Caelo    | Lycopodium herb, cut     | 11255012            | 2       |
| Caelo    | Lycopodium herb, cut     | 11255014            | 7       |
| Caelo    | Lycopodium herb, cut     | 1310502             | 1       |
| Caelo    | Lycopodium herb, cut     | 11255016            | 3       |
| Caelo    | Lycopodium herb, cut     | 11255017            | 6       |
| Caelo    | Lycopodium herb, cut     | 11255018            | 1       |
| Caelo    | Lycopodium herb, cut     | 9378812             | 1       |
| Caelo    | Lycopodium herb, cut     | 311122/1            | 1       |
| Caelo    | Magnesium chloride he... | 9L15-N01            | 1       |
| Caelo    | Magnesium chloride he... | 12141806            | 2       |
| Caelo    | Magnesium chloride he... | 12354615            | 9       |
| Caelo    | Magnesium chloride he... | 13194713-3490312103 | 1       |
| Caelo    | Magnesium chloride he... | 13194706            | 3       |
| Caelo    | Magnesium chloride he... | 12354618            | 2       |
| Caelo    | Magnesium chloride he... | 12354612            | 7       |
| Caelo    | Magnesium chloride he... | 12354609            | 7       |
| Caelo    | Magnesium chloride he... | 12141803            | 1       |
| Caelo    | Magnesium chloride he... | 12354605            | 5       |
| Caelo    | Magnesium chloride he... | 12141817            | 3       |
| Caelo    | Magnesium chloride he... | 12141814            | 1       |
| Caelo    | Magnesium chloride he... | 12354608            | 1       |
| Caelo    | Magnesium chloride he... | 12354606            | 5       |
| Caelo    | Magnesium chloride he... | 12141811            | 2       |
| Caelo    | Magnesium chloride he... | 12141808            | 1       |
| Caelo    | Magnesium chloride he... | 12354604            | 4       |
| Caelo    | Magnesium chloride he... | 11345624            | 2       |
| Caelo    | Magnesium chloride he... | 13194707            | 4       |
| Caelo    | Magnesium chloride he... | 11345615            | 1       |
| Caelo    | Magnesium chloride he... | 1021401             | 1       |
| Caelo    | Magnesium chloride he... | 1108024-01          | 2       |
| Caelo    | Magnesium chloride he... | 1.02.14             | 1       |
| Caelo    | Magnesium chloride he... | 11345623            | 2       |
| Caelo    | Magnesium chloride he... | 5210I-01828         | 1       |
| Caelo    | Magnesium chloride he... | 4013E-01828         | 1       |
| Caelo    | Magnesium chloride he... | 16094004            | 1       |
| Caelo    | Magnesium chloride he... | 1512I-01828         | 1       |
| Caelo    | Magnesium chloride he... | 13194721            | 2       |
| Caelo    | Magnesium chloride he... | 12354610            | 2       |
| Caelo    | Magnesium chloride he... | 11345606            | 1       |
| Caelo    | Magnesium chloride he... | 13194713            | 1       |
| Caelo    | Magnesium chloride he... | 12354613            | 7       |
| Caelo    | Magnesium chloride he... | 13194702            | 3       |
| Caelo    | Magnesium chloride he... | 13194701            | 1       |
| Caelo    | Magnesium chloride he... | 1304C004            | 2       |

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| Supplier | Substance                | Batch       | Spectra |
|----------|--------------------------|-------------|---------|
| Caelo    | Magnesium chloride he... | 11345609    | 1       |
| Caelo    | Magnesium sulfate hep... | 1218521     | 2       |
| Caelo    | Magnesium sulfate hep... | 12336916    | 3       |
| Caelo    | Magnesium sulfate hep... | 12336926    | 3       |
| Caelo    | Magnesium sulfate hep... | 12336942    | 1       |
| Caelo    | Magnesium sulfate hep... | 12c27-n06   | 1       |
| Caelo    | Magnesium sulfate hep... | 3612E-01835 | 1       |
| Caelo    | Magnesium sulfate hep... | 13183702    | 2       |
| Caelo    | Magnesium sulfate hep... | 13030107    | 1       |
| Caelo    | Magnesium sulfate hep... | 13030104    | 1       |
| Caelo    | Magnesium sulfate hep... | 13183709    | 2       |
| Caelo    | Magnesium sulfate hep... | 1213E-01835 | 1       |
| Caelo    | Magnesium sulfate hep... | 10371111    | 1       |
| Caelo    | Magnesium sulfate hep... | 12138515    | 2       |
| Caelo    | Magnesium sulfate hep... | 12336914    | 7       |
| Caelo    | Magnesium sulfate hep... | 12119906/2  | 1       |
| Caelo    | Magnesium sulfate hep... | 113695625   | 1       |
| Caelo    | Magnesium sulfate hep... | 12336915    | 4       |
| Caelo    | Magnesium sulfate hep... | 11369529    | 1       |
| Caelo    | Magnesium sulfate hep... | 11231025    | 2       |
| Caelo    | Magnesium sulfate hep... | 11231006    | 2       |
| Caelo    | Magnesium sulfate hep... | 11231005    | 1       |
| Caelo    | Magnesium sulfate hep... | 10104201    | 1       |
| Caelo    | Magnesium sulfate hep... | 6012014B    | 1       |
| Caelo    | Magnesium sulfate hep... | 11194001    | 1       |
| Caelo    | Magnesium sulfate hep... | 11369252    | 1       |
| Caelo    | Magnesium sulfate hep... | 12138522    | 2       |
| Caelo    | Magnesium sulfate hep... | 11369509    | 1       |
| Caelo    | Magnesium sulfate hep... | 90744129    | 1       |
| Caelo    | Magnesium sulfate hep... | 12138516    | 6       |
| Caelo    | Magnesium sulfate hep... | 11369526    | 17      |
| Caelo    | Magnesium sulfate hep... | 12119901/2  | 1       |
| Caelo    | Magnesium sulfate hep... | 11369525    | 7       |
| Caelo    | Magnesium sulfate hep... | 12138521    | 6       |
| Caelo    | Magnesium sulfate, dr... | 11265908    | 2       |
| Caelo    | Magnesium sulfate, dr... | 10213213    | 2       |
| Caelo    | Magnesium sulfate, dr... | 11265902    | 1       |
| Caelo    | Magnesium sulfate, dr... | 11265903    | 1       |
| Caelo    | Magnesium sulfate, dr... | 12157202    | 1       |
| Caelo    | Magnesium sulfate, dr... | 12157207    | 1       |
| Caelo    | Magnesium sulfate, dr... | 12157208    | 1       |
| Caelo    | Magnesium sulfate, dr... | M-220413-2  | 1       |
| Caelo    | Maize style, cut         | 10325902    | 3       |
| Caelo    | Maize style, cut         | 13277202    | 1       |
| Caelo    | Maize style, cut         | 13277207    | 1       |
| Caelo    | Maize style, cut         | 280363      | 1       |
| Caelo    | Maize style, cut         | 11280404    | 2       |
| Caelo    | Maize style, cut         | 10325907    | 4       |
| Caelo    | Maize style, cut         | 10325906    | 8       |
| Caelo    | Maize style, cut         | 10325904    | 2       |
| Caelo    | Maize style, cut         | 11280405    | 11      |
| Caelo    | Maize style, cut         | 13277205    | 1       |
| Caelo    | Maize style, cut         | 13381501    | 1       |
| Caelo    | Maize style, cut         | 13277201    | 1       |
| Caelo    | Maize style, cut         | 10325905    | 2       |
| Caelo    | Maize style, cut         | 3712Q-02333 | 1       |
| Caelo    | Male speedwell wort, ... | 12162503    | 3       |
| Caelo    | Male speedwell wort, ... | 1216504     | 1       |
| Caelo    | Male speedwell wort, ... | 20111303    | 1       |
| Caelo    | Male speedwell wort, ... | 25091203    | 1       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Male speedwell wort, ... | 4661c111011         | 1       |
| Caelo    | Male speedwell wort, ... | 12162505            | 1       |
| Caelo    | Male speedwell wort, ... | 12162504            | 13      |
| Caelo    | Male speedwell wort, ... | 13166701            | 3       |
| Caelo    | Male speedwell wort, ... | 11265504            | 1       |
| Caelo    | Male speedwell wort, ... | 11265502            | 4       |
| Caelo    | Male speedwell wort, ... | 11061305            | 1       |
| Caelo    | Male speedwell wort, ... | 3091305             | 1       |
| Caelo    | Male speedwell wort, ... | 3051306             | 1       |
| Caelo    | Male speedwell wort, ... | 28061303            | 1       |
| Caelo    | Male speedwell wort, ... | 2513A-01692         | 1       |
| Caelo    | Male speedwell wort, ... | 11265503            | 13      |
| Caelo    | Male speedwell wort, ... | 14111303            | 1       |
| Caelo    | Mallow flower, cut       | 10357902            | 3       |
| Caelo    | Mallow flower, cut       | 10357903            | 1       |
| Caelo    | Mallow flower, cut       | 11040101            | 2       |
| Caelo    | Mallow flower, cut       | 3912E-01464         | 1       |
| Caelo    | Mallow flower, cut       | Vorführprüfung      | 1       |
| Caelo    | Mallow flower, cut       | 12187402            | 12      |
| Caelo    | Mallow flower, cut       | 11040106            | 10      |
| Caelo    | Mallow flower, cut       | Nachprüfung         | 1       |
| Caelo    | Mallow flower, cut       | 23051205            | 1       |
| Caelo    | Mallow flower, cut       | 20061201            | 1       |
| Caelo    | Mallow flower, cut       | 9311104             | 1       |
| Caelo    | Mallow flower, cut       | 11040105            | 1       |
| Caelo    | Mallow flower, cut       | 27021301            | 1       |
| Caelo    | Mallow flower, cut       | 18111303            | 1       |
| Caelo    | Mallow flower, cut       | 13351309            | 1       |
| Caelo    | Mallow flower, cut       | 13351307            | 1       |
| Caelo    | Mallow flower, cut       | 13351303            | 2       |
| Caelo    | Mallow flower, cut       | 13351301            | 3       |
| Caelo    | Mallow flower, cut       | 8121202             | 1       |
| Caelo    | Mallow flower, cut       | 13267302            | 1       |
| Caelo    | Mallow flower, cut       | 13040402            | 1       |
| Caelo    | Mallow flower, cut       |                     | 1       |
| Caelo    | Mallow flower, cut       | 13267303            | 2       |
| Caelo    | Mallow flower, cut       | 12187401            | 1       |
| Caelo    | Mallow flower, cut       | 10357904            | 1       |
| Caelo    | Mallow flower, cut       | 12187405            | 4       |
| Caelo    | Mallow flower, cut       | 12187501            | 6       |
| Caelo    | Mallow flower, cut       | 12187502            | 1       |
| Caelo    | Mallow flower, cut       | 13267301            | 7       |
| Caelo    | Mallow flower, cut       | 13267301-3409310112 | 1       |
| Caelo    | Mallow flower, cut       | 12187501-3414310132 | 1       |
| Caelo    | Mallow flower, cut       | 12187404            | 6       |
| Caelo    | Mallow flower, cut       | 12187505            | 2       |
| Caelo    | Mallow leaf, cut         | 13174217            | 1       |
| Caelo    | Mallow leaf, cut         | 1412M-01501         | 1       |
| Caelo    | Mallow leaf, cut         | 28061203            | 1       |
| Caelo    | Mallow leaf, cut         | 13174213            | 1       |
| Caelo    | Mallow leaf, cut         | 3912A-01501         | 1       |
| Caelo    | Mallow leaf, cut         | 20111302            | 1       |
| Caelo    | Mallow leaf, cut         | 13174207            | 1       |
| Caelo    | Mallow leaf, cut         | 14073902            | 1       |
| Caelo    | Mallow leaf, cut         | 12310008            | 1       |
| Caelo    | Mallow leaf, cut         | 12310001            | 3       |
| Caelo    | Mallow leaf, cut         | 10290510            | 1       |
| Caelo    | Mallow leaf, cut         | 12153403            | 1       |
| Caelo    | Mallow leaf, cut         | 12310009            | 2       |
| Caelo    | Mallow leaf, cut         | 12310004            | 5       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>    | <b>Spectra</b> |
|-----------------|--------------------------|-----------------|----------------|
| Caelo           | Mallow leaf, cut         | 10290517        | 1              |
| Caelo           | Mallow leaf, cut         | 12310006        | 1              |
| Caelo           | Mallow leaf, cut         | 10290502        | 2              |
| Caelo           | Mallow leaf, cut         | 10290515        | 1              |
| Caelo           | Manganese sulfate mon... | 123825          | 1              |
| Caelo           | Manganese sulfate mon... | 91547399        | 1              |
| Caelo           | Manna, cut               | 1308913         | 1              |
| Caelo           | Manna, cut               | 15219005        | 1              |
| Caelo           | Manna, cut               | 11061404        | 1              |
| Caelo           | Manna, cut               | 11308911        | 4              |
| Caelo           | Manna, cut               | 15219010        | 1              |
| Caelo           | Manna, cut               | 14001305        | 1              |
| Caelo           | Manna, cut               | 25071403        | 1              |
| Caelo           | Manna, cut               | 13127003        | 6              |
| Caelo           | Manna, cut               | 14001315        | 1              |
| Caelo           | Manna, cut               | 14001303        | 3              |
| Caelo           | Manna, cut               | 28101404        | 1              |
| Caelo           | Manna, cut               | 14001310        | 1              |
| Caelo           | Manna, cut               | 2713M-01843     | 1              |
| Caelo           | Manna, cut               | 25111301        | 1              |
| Caelo           | Manna, cut               | 11308901        | 2              |
| Caelo           | Manna, cut               | 14001308        | 1              |
| Caelo           | Manna, cut               | 11308907        | 6              |
| Caelo           | Manna, cut               | 11308909        | 2              |
| Caelo           | Manna, cut               | 11041401        | 1              |
| Caelo           | Manna, powdered          | 11003611        | 1              |
| Caelo           | Manna, powdered          | 11308802        | 2              |
| Caelo           | Manna, powdered          | 15101306        | 1              |
| Caelo           | Manna, powdered          | 14001402        | 1              |
| Caelo           | Manna, powdered          | 15101312        | 1              |
| Caelo           | Manna, powdered          | 11308909        | 1              |
| Caelo           | Manna, powdered          | 11308807        | 1              |
| Caelo           | Manna, powdered          | 11308907        | 1              |
| Caelo           | Manna, powdered          | 11071311        | 1              |
| Caelo           | Marian thistle fruit     | 12189106        | 4              |
| Caelo           | Marian thistle fruit     | 10270613        | 1              |
| Caelo           | Marian thistle fruit     | 10270614        | 5              |
| Caelo           | Marian thistle fruit     | 12189113        | 8              |
| Caelo           | Marian thistle fruit     | 10270615        | 4              |
| Caelo           | Marian thistle fruit     | 15409204        | 2              |
| Caelo           | Marian thistle fruit     | 12189115        | 4              |
| Caelo           | Marian thistle fruit     | 13326202        | 3              |
| Caelo           | Marian thistle fruit     | 13342003        | 1              |
| Caelo           | Marian thistle fruit     | 12189116        | 2              |
| Caelo           | Marian thistle fruit     | 27111203        | 1              |
| Caelo           | Marian thistle fruit     | 12198107        | 1              |
| Caelo           | Marian thistle fruit     | 1289112         | 2              |
| Caelo           | Marian thistle fruit     | 10270612        | 2              |
| Caelo           | Marian thistle fruit     | 18111301        | 1              |
| Caelo           | Marian thistle fruit     | 1126705         | 1              |
| Caelo           | Marian thistle fruit     | 12189111        | 5              |
| Caelo           | Marian thistle fruit     | 12189112        | 14             |
| Caelo           | Marian thistle fruit     | 1126704         | 1              |
| Caelo           | Marian thistle fruit     | 12189104        | 4              |
| Caelo           | Marian thistle fruit     | 46111-02233     | 1              |
| Caelo           | Marian thistle fruit     | Ch.B. :11126702 | 1              |
| Caelo           | Marian thistle fruit     | 12189107        | 3              |
| Caelo           | Marian thistle fruit     | 11126703        | 3              |
| Caelo           | Marian thistle fruit     | 912a-02233      | 1              |
| Caelo           | Marian thistle fruit     | 10270610        | 3              |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Marian thistle fruit     | 11126701            | 2       |
| Caelo    | Marian thistle fruit     | 1126703             | 1       |
| Caelo    | Marian thistle fruit     | 12189108            | 4       |
| Caelo    | Marian thistle fruit     | 12189105            | 9       |
| Caelo    | Marian thistle fruit     | 11126701,           | 1       |
| Caelo    | Marian thistle fruit     | 12189109            | 4       |
| Caelo    | Marian thistle fruit     | 11126705            | 3       |
| Caelo    | Marian thistle herb, ... | 10315907            | 1       |
| Caelo    | Marian thistle herb, ... | 10365601            | 9       |
| Caelo    | Marian thistle herb, ... | 13130701-3492411030 | 1       |
| Caelo    | Marian thistle herb, ... | 10365603            | 1       |
| Caelo    | Marian thistle herb, ... | 10365605            | 1       |
| Caelo    | Marian thistle herb, ... | 1035911             | 1       |
| Caelo    | Marian thistle herb, ... | 10365604            | 5       |
| Caelo    | Marian thistle herb, ... | 10315906            | 1       |
| Caelo    | Marian thistle herb, ... | 30101306            | 1       |
| Caelo    | Marian thistle herb, ... | 10315910            | 1       |
| Caelo    | Marian thistle herb, ... | 17121204            | 1       |
| Caelo    | Marian thistle herb, ... | 13130703            | 2       |
| Caelo    | Marian thistle herb, ... | 62607127            | 1       |
| Caelo    | Marian thistle herb, ... | 13130701            | 3       |
| Caelo    | Marian thistle herb, ... | 13386703-3543411013 | 1       |
| Caelo    | Marian thistle herb, ... | intch:318080        | 1       |
| Caelo    | Marian thistle herb, ... | 10365602            | 3       |
| Caelo    | Marian thistle herb, ... |                     | 1       |
| Caelo    | Marian thistle herb, ... | 1313702             | 1       |
| Caelo    | Marian thistle herb, ... | 13130704            | 5       |
| Caelo    | Marian thistle herb, ... | 13130702            | 5       |
| Caelo    | Marian thistle herb, ... | 10315911            | 5       |
| Caelo    | Marian thistle herb, ... | 18041303            | 1       |
| Caelo    | Marian thistle herb, ... | 10315909            | 2       |
| Caelo    | Marjoram herb, rubbed    | 9292602             | 1       |
| Caelo    | Marjoram herb, rubbed    | 13113304            | 3       |
| Caelo    | Marjoram herb, rubbed    | 13113310            | 1       |
| Caelo    | Marjoram herb, rubbed    | 11212708            | 2       |
| Caelo    | Marjoram herb, rubbed    | 6051302             | 1       |
| Caelo    | Marjoram herb, rubbed    | 11212710            | 1       |
| Caelo    | Marjoram herb, rubbed    | 11212711            | 3       |
| Caelo    | Marjoram herb, rubbed    | 11212713            | 1       |
| Caelo    | Marjoram herb, rubbed    | 27011402            | 1       |
| Caelo    | Marjoram herb, rubbed    | 11212704            | 1       |
| Caelo    | Marjoram herb, rubbed    | 12168902            | 1       |
| Caelo    | Marjoram herb, rubbed    | 11212707            | 2       |
| Caelo    | Marjoram herb, rubbed    | 12168901            | 5       |
| Caelo    | Marjoram herb, rubbed    | 12168904            | 1       |
| Caelo    | Marjoram herb, rubbed    | 13113303            | 3       |
| Caelo    | Marjoram herb, rubbed    | 12168910            | 10      |
| Caelo    | Marjoram herb, rubbed    | 12168912            | 1       |
| Caelo    | Marjoram herb, rubbed    | 12168908            | 9       |
| Caelo    | Marjoram herb, rubbed    | 12168909            | 5       |
| Caelo    | Marjoram herb, rubbed    | 12168907            | 4       |
| Caelo    | Marjoram herb, rubbed    | 12168906            | 3       |
| Caelo    | Marjoram herb, rubbed    | 12168905            | 2       |
| Caelo    | Marjoram herb, rubbed    | 12168903            | 11      |
| Caelo    | Marrubium vulgare her... | 11253802            | 1       |
| Caelo    | Marrubium vulgare her... | 12231601            | 3       |
| Caelo    | Marrubium vulgare her... | 1153803             | 1       |
| Caelo    | Marrubium vulgare her... | 313091              | 1       |
| Caelo    | Marrubium vulgare her... | 12231604            | 5       |
| Caelo    | Marrubium vulgare her... | 11253803            | 1       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Marrubium vulgare her... | 12231605            | 4       |
| Caelo    | Marrubium vulgare her... | 12231603            | 1       |
| Caelo    | Marrubium vulgare her... | 13289109            | 1       |
| Caelo    | Marshmallow leaf, cut    | 12328206            | 4       |
| Caelo    | Marshmallow leaf, cut    | 12328207            | 2       |
| Caelo    | Marshmallow leaf, cut    | 12328202            | 3       |
| Caelo    | Marshmallow leaf, cut    | 11101002            | 1       |
| Caelo    | Marshmallow root, nat... | 270114              | 1       |
| Caelo    | Marshmallow root, pee... | 11101907            | 8       |
| Caelo    | Marshmallow root, pee... | 12147311            | 6       |
| Caelo    | Marshmallow root, pee... | 15104503            | 1       |
| Caelo    | Marshmallow root, pee... | 26091201            | 1       |
| Caelo    | Marshmallow root, pee... | 11101804            | 2       |
| Caelo    | Marshmallow root, pee... | 13057103            | 1       |
| Caelo    | Marshmallow root, pee... | nachprüfung         | 1       |
| Caelo    | Marshmallow root, pee... | 11101804            | 1       |
| Caelo    | Marshmallow root, pee... | 11101808            | 1       |
| Caelo    | Marshmallow root, pee... | 11101809            | 1       |
| Caelo    | Marshmallow root, pee... | 11101905            | 1       |
| Caelo    | Marshmallow root, pee... | 11101906            | 1       |
| Caelo    | Marshmallow root, pee... | 11101907            | 1       |
| Caelo    | Marshmallow root, pee... | 12147311            | 1       |
| Caelo    | Marshmallow root, pee... | 12147310            | 1       |
| Caelo    | Marshmallow root, pee... | 6071A130408         | 12      |
| Caelo    | Marshmallow root, pee... | 12368906            | 1       |
| Caelo    | Masterwort root, cut     | 12101804            | 1       |
| Caelo    | Masterwort root, cut     | 13341201            | 1       |
| Caelo    | Masterwort root, cut     | 12101806            | 2       |
| Caelo    | Masterwort root, cut     | 13132002            | 1       |
| Caelo    | Masterwort root, cut     | 12101808            | 1       |
| Caelo    | Masterwort root, cut     | 1210801             | 1       |
| Caelo    | Masterwort root, cut     | 12101807            | 2       |
| Caelo    | Maté leaf, cut           | 13118003            | 4       |
| Caelo    | Maté leaf, cut           | 12133806            | 1       |
| Caelo    | Maté leaf, cut           | 12133801            | 3       |
| Caelo    | Maté leaf, cut           | 13061202            | 1       |
| Caelo    | Maté leaf, cut           | 12133804            | 7       |
| Caelo    | Maté leaf, cut           | 12133807            | 8       |
| Caelo    | Maté leaf, cut           | 13118001            | 1       |
| Caelo    | Maté leaf, cut           | 12133803            | 3       |
| Caelo    | Maté leaf, cut           | 2141A111213         | 18      |
| Caelo    | Maté leaf, cut           | 11091703            | 1       |
| Caelo    | Maté leaf, cut           | 11091710            | 1       |
| Caelo    | Matricaria flower        | 12244804            | 2       |
| Caelo    | Matricaria flower        | 12244803            | 1       |
| Caelo    | Matricaria flower        | 22081202            | 1       |
| Caelo    | Matricaria flower        | 13210901-3478312171 | 1       |
| Caelo    | Matricaria flower        | 12294802            | 19      |
| Caelo    | Matricaria flower        | 12244803            | 4       |
| Caelo    | Matricaria flower        | 12244802            | 6       |
| Caelo    | Matricaria flower        | 315I-01452          | 1       |
| Caelo    | Matricaria flower        | 12111904            | 2       |
| Caelo    | Matricaria flower        | 11169607            | 1       |
| Caelo    | Matricaria flower        | 121111903           | 1       |
| Caelo    | Matricaria flower        | 11218501            | 1       |
| Caelo    | Matricaria flower        | 11214810            | 1       |
| Caelo    | Matricaria flower        | 11214805            | 1       |
| Caelo    | Matricaria flower        | 11101203            | 1       |
| Caelo    | Matricaria flower        | 10081201            | 1       |
| Caelo    | Matricaria flower        | 5081201             | 1       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Matricaria flower        | 2914A-01452         | 1       |
| Caelo    | Matricaria flower        | 12244602            | 1       |
| Caelo    | Matricaria flower        | 12294802            | 1       |
| Caelo    | Matricaria flower        | 12294804            | 1       |
| Caelo    | Matricaria flower        | 12299703            | 2       |
| Caelo    | Matricaria flower        | 12337601            | 2       |
| Caelo    | Matricaria flower        | 12337607            | 3       |
| Caelo    | Matricaria flower        | 12337608            | 2       |
| Caelo    | Matricaria flower        | 12361706            | 1       |
| Caelo    | Matricaria flower        | 12361707            | 2       |
| Caelo    | Matricaria flower        | 13061201            | 1       |
| Caelo    | Matricaria flower        | 13210905            | 1       |
| Caelo    | Matricaria flower        | 13288403            | 1       |
| Caelo    | Matricaria flower        | 13288405            | 3       |
| Caelo    | Matricaria flower        | 1229804             | 1       |
| Caelo    | Matricaria flower        | 11214802            | 3       |
| Caelo    | Matricaria flower        | 12299701            | 1       |
| Caelo    | Matricaria flower        | 12361704            | 1       |
| Caelo    | Matricaria flower        | 13210901-3546411013 | 1       |
| Caelo    | Matricaria flower        | IntCh:313011        | 1       |
| Caelo    | Matricaria flower        | AKD5                | 1       |
| Caelo    | Matricaria flower        | 31051314            | 1       |
| Caelo    | Matricaria flower        | 27091203            | 1       |
| Caelo    | Matricaria flower        | 26081303            | 1       |
| Caelo    | Matricaria flower        | 22111202            | 1       |
| Caelo    | Matricaria flower        | 22111201            | 1       |
| Caelo    | Matricaria flower        | 22011303            | 1       |
| Caelo    | Matricaria flower        | 20021313            | 1       |
| Caelo    | Matricaria flower        | 19111207            | 1       |
| Caelo    | Matricaria flower        | 19041306            | 1       |
| Caelo    | Matricaria flower        | 17101204            | 1       |
| Caelo    | Matricaria flower        | 16111202            | 1       |
| Caelo    | Matricaria flower        | 15258505            | 1       |
| Caelo    | Matricaria flower        | 15258504            | 1       |
| Caelo    | Matricaria flower        | 15090003            | 2       |
| Caelo    | Matricaria flower        | 14276804            | 3       |
| Caelo    | Matricaria flower        | 13210906            | 1       |
| Caelo    | Matricaria flower        | 13210905            | 3       |
| Caelo    | Matricaria flower        | 13210903            | 1       |
| Caelo    | Matricaria flower        | 13210901            | 3       |
| Caelo    | Matricaria flower        | 13111201            | 1       |
| Caelo    | Matricaria flower        | 13031306            | 1       |
| Caelo    | Matricaria flower        | 13011406            | 1       |
| Caelo    | Matricaria flower        | 12361707            | 5       |
| Caelo    | Matricaria flower        | 12361706            | 3       |
| Caelo    | Matricaria flower        | 12361701            | 4       |
| Caelo    | Matricaria flower        | 12059606            | 2       |
| Caelo    | Matricaria flower        | 13288410            | 1       |
| Caelo    | Meadowsweet flower, r... | 10349307            | 2       |
| Caelo    | Meadowsweet flower, r... | 17121-03283         | 1       |
| Caelo    | Meadowsweet flower, r... | 12275706            | 1       |
| Caelo    | Meadowsweet flower, r... | 12275704            | 4       |
| Caelo    | Meadowsweet flower, r... | 1227501             | 1       |
| Caelo    | Meadowsweet flower, r... | 1225702             | 1       |
| Caelo    | Meadowsweet flower, r... | 10349306            | 1       |
| Caelo    | Meadowsweet flower, r... | 10051301            | 1       |
| Caelo    | Meadowsweet flower, r... | 10349305            | 1       |
| Caelo    | Meadowsweet flower, r... | 12275701            | 2       |
| Caelo    | Meadowsweet flower, r... | 12275703            | 5       |
| Caelo    | Meadowsweet flower, r... | 12275704-3372319032 | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b> | <b>Spectra</b> |
|-----------------|--------------------------|--------------|----------------|
| Caelo           | Meadowsweet flower, r... | 10349302     | 3              |
| Caelo           | Meadowsweet flower, r... | 9326213      | 3              |
| Caelo           | Meadowsweet flower, r... | 9326211      | 2              |
| Caelo           | Meadowsweet flower, r... | 82230309     | 1              |
| Caelo           | Meadowsweet herb, cut    | 12188801     | 1              |
| Caelo           | Meadowsweet herb, cut    | 12188806     | 3              |
| Caelo           | Meadowsweet herb, cut    | 12188803     | 10             |
| Caelo           | Meadowsweet herb, cut    | 12188807     | 1              |
| Caelo           | Meadowsweet herb, cut    | 12188704     | 1              |
| Caelo           | Meadowsweet herb, cut    | 62487517     | 1              |
| Caelo           | Meadowsweet herb, cut    | 12188702     | 1              |
| Caelo           | Meadowsweet herb, cut    | 19071203     | 1              |
| Caelo           | Meadowsweet herb, cut    | 10381601     | 2              |
| Caelo           | Meadowsweet herb, cut    | 12188805     | 12             |
| Caelo           | Meadowsweet herb, cut    | 12188703     | 2              |
| Caelo           | Meadowsweet herb, cut    | 4912E-01685  | 1              |
| Caelo           | Melilot herb, cut        | 12289202     | 10             |
| Caelo           | Melilot herb, cut        | 12289205     | 3              |
| Caelo           | Melilot herb, cut        | nachprüfung  | 1              |
| Caelo           | Melilot herb, cut        | 25101205     | 1              |
| Caelo           | Melilot herb, cut        | 25091301     | 1              |
| Caelo           | Melilot herb, cut        | 24081202     | 1              |
| Caelo           | Melilot herb, cut        | 22111303     | 1              |
| Caelo           | Melilot herb, cut        | 12289207     | 1              |
| Caelo           | Melilot herb, cut        | 12289206     | 1              |
| Caelo           | Melilot herb, cut        | 11307601     | 4              |
| Caelo           | Melilot herb, cut        | 12289203     | 5              |
| Caelo           | Melilot herb, cut        | 12289201     | 1              |
| Caelo           | Melilot herb, cut        | 12289003     | 1              |
| Caelo           | Melilot herb, cut        | 11307607     | 2              |
| Caelo           | Melilot herb, cut        | 107063       | 1              |
| Caelo           | Melilot herb, cut        | 10335410     | 1              |
| Caelo           | Melilot herb, cut        | 10335403     | 1              |
| Caelo           | Melilot herb, cut        | 612M-01664   | 1              |
| Caelo           | Melilot herb, cut        | 19071201     | 1              |
| Caelo           | Melilot herb, cut        | 11307602     | 2              |
| Caelo           | Melilot herb, cut        | 8061204      | 1              |
| Caelo           | Melilot herb, cut        | 12231703     | 3              |
| Caelo           | Melilot herb, cut        | 11307606     | 9              |
| Caelo           | Melissa leaf, cut        |              | 3              |
| Caelo           | Melissa leaf, cut        | 24011407     | 1              |
| Caelo           | Melissa leaf, cut        | 25021301     | 1              |
| Caelo           | Melissa leaf, cut        | 25061303     | 1              |
| Caelo           | Melissa leaf, cut        | CH.111111    | 1              |
| Caelo           | Melissa leaf, cut        | 2161a121009  | 1              |
| Caelo           | Melissa leaf, cut        | 2161a120718  | 1              |
| Caelo           | Melissa leaf, cut        | 13030801     | 1              |
| Caelo           | Melissa leaf, cut        | 12032303     | 3              |
| Caelo           | Melissa leaf, cut        | 15121705     | 2              |
| Caelo           | Melissa leaf, cut        | 10310921     | 1              |
| Caelo           | Melissa leaf, cut        | 1009         | 1              |
| Caelo           | Melissa leaf, cut        | 12032302     | 1              |
| Caelo           | Melissa leaf, cut        | 14221705     | 1              |
| Caelo           | Melissa leaf, cut        | 14221701     | 2              |
| Caelo           | Melissa leaf, cut        | 12032307     | 2              |
| Caelo           | Melissa leaf, cut        | 12032308     | 1              |
| Caelo           | Melissa leaf, cut        | 13030803     | 2              |
| Caelo           | Melissa leaf, cut        | 12032309     | 2              |
| Caelo           | Melissa leaf, cut        | 14111319     | 1              |
| Caelo           | Melissa leaf, cut        | 13214720     | 2              |

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| Supplier | Substance                | Batch            | Spectra |
|----------|--------------------------|------------------|---------|
| Caelo    | Melissa leaf, cut        | 13214707         | 1       |
| Caelo    | Melissa leaf, cut        | 13214705         | 2       |
| Caelo    | Melissa leaf, cut        | 13030805         | 1       |
| Caelo    | Melissa leaf, cut        | 12032315         | 1       |
| Caelo    | Melissa leaf, cut        | 12032316         | 3       |
| Caelo    | Melissa leaf, cut        | 12032319         | 5       |
| Caelo    | Melissa leaf, cut        | 12032311         | 1       |
| Caelo    | Melissa leaf, cut        | 10310919         | 1       |
| Caelo    | Melissa leaf, cut        | 13030804         | 1       |
| Caelo    | Melissa leaf, cut        | 15350306         | 1       |
| Caelo    | Melissa leaf, cut        | 12032314         | 8       |
| Caelo    | Melissa leaf, cut        | 19041303         | 1       |
| Caelo    | Melissa leaf, cut        | 12032310         | 2       |
| Caelo    | Melissa leaf, cut        | 10310918         | 1       |
| Caelo    | Melissa leaf, cut        | 10310914         | 1       |
| Caelo    | Melissa leaf, cut        | 10310912         | 1       |
| Caelo    | Melissa leaf, cut        | 1535036          | 1       |
| Caelo    | Melissa leaf, cut        | 15121708         | 2       |
| Caelo    | Methadone hydrochloride  | 12344819         | 1       |
| Caelo    | Methadone hydrochloride  | 16135310         | 1       |
| Caelo    | Methadone hydrochloride  | 15244702         | 1       |
| Caelo    | Methadone hydrochloride  | 12344802         | 1       |
| Caelo    | Methadone hydrochloride  | 13266511         | 1       |
| Caelo    | Methadone hydrochloride  | 12344812         | 2       |
| Caelo    | Methadone hydrochloride  | 17011406         | 1       |
| Caelo    | Methadone hydrochloride  | 12171902         | 1       |
| Caelo    | Methadone hydrochloride  | 15244720         | 1       |
| Caelo    | Methadone hydrochloride  | 12171906         | 2       |
| Caelo    | Methadone hydrochloride  | 16135308         | 2       |
| Caelo    | Methadone hydrochloride  | 12171918         | 1       |
| Caelo    | Methadone hydrochloride  | 16135311         | 1       |
| Caelo    | Methadone hydrochloride  | 16135318         | 2       |
| Caelo    | Methadone hydrochloride  | 16135319         | 1       |
| Caelo    | Methadone hydrochloride  | 12171914         | 1       |
| Caelo    | Methadone hydrochloride  | 12171907         | 1       |
| Caelo    | Methadone hydrochloride  | 10076407         | 1       |
| Caelo    | Methadone hydrochloride  | 11227507         | 1       |
| Caelo    | Methadone hydrochloride  | 12344814         | 2       |
| Caelo    | Methadone hydrochloride  | 16135326         | 1       |
| Caelo    | Methadone hydrochloride  | 12344816         | 3       |
| Caelo    | Methadone hydrochloride  | 13266518         | 3       |
| Caelo    | Methadone hydrochloride  | 15215501         | 1       |
| Caelo    | Methadone hydrochloride  | 14C24-B01-292860 | 1       |
| Caelo    | Methadone hydrochloride  | 1327H051         | 1       |
| Caelo    | Methadone hydrochloride  | 13266521         | 1       |
| Caelo    | Methadone hydrochloride  | 15244709         | 2       |
| Caelo    | Methadone hydrochloride  | 13266515         | 1       |
| Caelo    | Methadone hydrochloride  | 13266512         | 2       |
| Caelo    | Methadone hydrochloride  | 13266509         | 1       |
| Caelo    | Methadone hydrochloride  | 13266505         | 4       |
| Caelo    | Methadone hydrochloride  | 13266504         | 2       |
| Caelo    | Methadone hydrochloride  | 13266502         | 2       |
| Caelo    | Methadone hydrochloride  | 13266501         | 1       |
| Caelo    | Methadone hydrochloride  | 12344821         | 2       |
| Caelo    | Methadone hydrochloride  | 12344807         | 1       |
| Caelo    | Methadone hydrochloride  | 12344818         | 2       |
| Caelo    | Methadone hydrochloride  | 15244705         | 1       |
| Caelo    | Methadone hydrochloride  | 15244706         | 3       |
| Caelo    | Methadone hydrochloride  | 12344810         | 1       |
| Caelo    | Methylrosanilinium ch... | 9238109          | 1       |

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| Supplier | Substance                | Batch         | Spectra |
|----------|--------------------------|---------------|---------|
| Caelo    | Methylrosanilinium ch... | 9238107       | 2       |
| Caelo    | Methylrosanilinium ch... | 9238106       | 1       |
| Caelo    | Methylrosanilinium ch... | 13184801      | 1       |
| Caelo    | Methylrosanilinium ch... | 12/17-N05     | 1       |
| Caelo    | Methylrosanilinium ch... | 12H28-N06     | 2       |
| Caelo    | Methylrosanilinium ch... | 13H28-N03     | 18      |
| Caelo    | Methylrosanilinium ch... | 8088701       | 1       |
| Caelo    | Methylrosanilinium ch... | 12H28-No6     | 1       |
| Caelo    | Midazolam hydrochloride  | 2061508       | 1       |
| Caelo    | Midazolam hydrochloride  | 1225811       | 3       |
| Caelo    | Midazolam hydrochloride  | 133370003     | 1       |
| Caelo    | Midazolam hydrochloride  | 14339002      | 1       |
| Caelo    | Midazolam hydrochloride  | 11184705      | 1       |
| Caelo    | Midazolam hydrochloride  | 14339008      | 2       |
| Caelo    | Midazolam hydrochloride  | 14339009      | 1       |
| Caelo    | Midazolam hydrochloride  | 14339015      | 1       |
| Caelo    | Midazolam hydrochloride  | 15224605      | 1       |
| Caelo    | Midazolam hydrochloride  | 15224607      | 1       |
| Caelo    | Midazolam hydrochloride  | 13370007      | 1       |
| Caelo    | Midazolam hydrochloride  | 15224614      | 1       |
| Caelo    | Midazolam hydrochloride  | 12094512      | 1       |
| Caelo    | Mistletoe, cut           | 29101302      | 1       |
| Caelo    | Mistletoe, cut           | 14292514      | 1       |
| Caelo    | Mistletoe, cut           | 14292506      | 2       |
| Caelo    | Mistletoe, cut           | 10273407      | 3       |
| Caelo    | Mistletoe, cut           | 14034209      | 1       |
| Caelo    | Mistletoe, cut           | 1266711       | 1       |
| Caelo    | Mistletoe, cut           | 18031303      | 1       |
| Caelo    | Mistletoe, cut           | 20121303      | 1       |
| Caelo    | Mistletoe, cut           | 26071302      | 1       |
| Caelo    | Mistletoe, cut           | 29071302      | 1       |
| Caelo    | Mistletoe, cut           | 23111204      | 1       |
| Caelo    | Mistletoe, cut           | 4313E-01695   | 1       |
| Caelo    | Mistletoe, cut           | 12011301      | 1       |
| Caelo    | Mistletoe, cut           | 27121305      | 1       |
| Caelo    | Mistletoe, cut           | 28101304      | 1       |
| Caelo    | Mistletoe, cut           | 29061201      | 1       |
| Caelo    | Mistletoe, cut           | 11294004      | 6       |
| Caelo    | Mistletoe, cut           | 3813E-01695   | 1       |
| Caelo    | Mistletoe, cut           | 11294003      | 3       |
| Caelo    | Mistletoe, cut           | 24011401      | 1       |
| Caelo    | Mistletoe, cut           | 29081302      | 1       |
| Caelo    | Mistletoe, cut           | 11294005      | 16      |
| Caelo    | Mistletoe, cut           | 11266708      | 9       |
| Caelo    | Mistletoe, cut           | 11021303      | 1       |
| Caelo    | Mistletoe, cut           | 11266702      | 4       |
| Caelo    | Mistletoe, cut           | 1027342010-13 | 1       |
| Caelo    | Mistletoe, cut           | 10273420      | 9       |
| Caelo    | Mistletoe, cut           | 11266714      | 4       |
| Caelo    | Mistletoe, cut           | 10273418      | 1       |
| Caelo    | Mistletoe, cut           | 10273412      | 4       |
| Caelo    | Mistletoe, cut           | 11266703      | 7       |
| Caelo    | Mistletoe, cut           | 11266705      | 6       |
| Caelo    | Mistletoe, cut           | 6061306       | 1       |
| Caelo    | Mistletoe, cut           | 11266713      | 2       |
| Caelo    | Mistletoe, cut           | 10091201      | 1       |
| Caelo    | Mistletoe, cut           | 11294002      | 3       |
| Caelo    | Mistletoe, cut           | 10081205      | 1       |
| Caelo    | Mistletoe, cut           | 11266712      | 11      |
| Caelo    | Mistletoe, cut           | 17061304      | 1       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Mistletoe, cut           | 11266704            | 16      |
| Caelo    | Mistletoe, cut           | 11266709            | 9       |
| Caelo    | Mistletoe, cut           | 11266712-3450311162 | 1       |
| Caelo    | Mistletoe, cut           | 11266710            | 7       |
| Caelo    | Molecular distilled g... | 11160012            | 1       |
| Caelo    | Morphine hydrochloride   | 13081310            | 1       |
| Caelo    | Morphine hydrochloride   | 13125206            | 1       |
| Caelo    | Morphine hydrochloride   | 12104409            | 1       |
| Caelo    | Morphine hydrochloride   | 12104403            | 1       |
| Caelo    | Morphine hydrochloride   | 14055084            | 1       |
| Caelo    | Morphine hydrochloride   | 14238604            | 1       |
| Caelo    | Morphine hydrochloride   | 14238617            | 1       |
| Caelo    | Morphine hydrochloride   | 12318101            | 1       |
| Caelo    | Morphine hydrochloride   | 15199705            | 1       |
| Caelo    | Morphine hydrochloride   | 15199705Nr. 2       | 1       |
| Caelo    | Morphine hydrochloride   | 14238619            | 1       |
| Caelo    | Morphine hydrochloride   | 15199711            | 4       |
| Caelo    | Morphine hydrochloride   | 1543904             | 1       |
| Caelo    | Morphine hydrochloride   | 15439405            | 2       |
| Caelo    | Morphine hydrochloride   | 15439409            | 1       |
| Caelo    | Morphine hydrochloride   | 15199705Nr. 3       | 1       |
| Caelo    | Motherwort herb, cut     | 12376403            | 1       |
| Caelo    | Motherwort herb, cut     | 12376402            | 1       |
| Caelo    | Motherwort herb, cut     | 12376407            | 1       |
| Caelo    | Motherwort herb, cut     | 12231503            | 2       |
| Caelo    | Motherwort herb, cut     | 12376408            | 2       |
| Caelo    | Motherwort herb, cut     | nachprüfung         | 1       |
| Caelo    | Motherwort herb, cut     | 11293004            | 3       |
| Caelo    | Motherwort herb, cut     | 5061203             | 1       |
| Caelo    | Motherwort herb, cut     | 2712E-01658         | 1       |
| Caelo    | Motherwort herb, cut     | 11293003            | 1       |
| Caelo    | Motherwort herb, cut     | 10244610            | 1       |
| Caelo    | Motherwort herb, cut     | 12231502            | 3       |
| Caelo    | Mullein flower, cut      | 11233401            | 6       |
| Caelo    | Mullein flower, cut      | 1219203             | 1       |
| Caelo    | Mullein flower, cut      | 16081201            | 1       |
| Caelo    | Mullein flower, cut      | 12170901            | 1       |
| Caelo    | Mullein flower, cut      | 11233402            | 1       |
| Caelo    | Mullein flower, cut      | 11020711            | 1       |
| Caelo    | Mullein flower, cut      | 613M-01475          | 1       |
| Caelo    | Mullein flower, cut      | 11020902            | 1       |
| Caelo    | Mullein flower, cut      | 11020802            | 2       |
| Caelo    | Mullein flower, cut      | 10156901            | 1       |
| Caelo    | Mullein flower, cut      | 13229701            | 2       |
| Caelo    | Mullein flower, cut      | 13229702            | 1       |
| Caelo    | Mullein flower, cut      | 12192901            | 4       |
| Caelo    | Mullein flower, cut      | 12192903            | 6       |
| Caelo    | Mullein flower, cut      | 11020713            | 5       |
| Caelo    | Mullein flower, cut      | 12192904            | 1       |
| Caelo    | Mullein flower, cut      | 12192905            | 7       |
| Caelo    | Mullein flower, cut      | 12192907            | 4       |
| Caelo    | Mullein flower, cut      | 18031301            | 1       |
| Caelo    | Mullein flower, cut      | 521505390           | 1       |
| Caelo    | Mullein flower, cut      | 12192902            | 1       |
| Caelo    | Mullein flower, cut      | 12317104            | 1       |
| Caelo    | Mullein flower, cut      | 12170906            | 1       |
| Caelo    | Mullein flower, cut      | 11333402            | 1       |
| Caelo    | Mullein flower, cut      | 11366402            | 1       |
| Caelo    | Mullein flower, cut      | 12170903            | 3       |
| Caelo    | Mullein flower, cut      | 11366403            | 3       |

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| Supplier | Substance           | Batch               | Spectra |
|----------|---------------------|---------------------|---------|
| Caelo    | Mullein flower, cut | 11020708            | 1       |
| Caelo    | Myrrh               | 12244404            | 1       |
| Caelo    | Myrrh               | 13108701            | 3       |
| Caelo    | Myrrh               | 12305709            | 1       |
| Caelo    | Myrrh               | 12269913            | 1       |
| Caelo    | Myrrh               | 14244602            | 1       |
| Caelo    | Myrrh               | 11277105            | 1       |
| Caelo    | Myrrh               | 12269906            | 1       |
| Caelo    | Myrrh               | 12269904            | 4       |
| Caelo    | Myrrh               | 28101401            | 1       |
| Caelo    | Myrrh               | 30121413            | 1       |
| Caelo    | Myrrh               | 12269901            | 2       |
| Caelo    | Myrrh               | 11277111            | 1       |
| Caelo    | Myrrh               | 11276810            | 1       |
| Caelo    | Myrrh               | 11277111            | 1       |
| Caelo    | Myrrh               | 15189202            | 1       |
| Caelo    | Myrrh               | 12269907            | 1       |
| Caelo    | Myrrh               | 12244411            | 1       |
| Caelo    | Myrrh               | 11276811            | 2       |
| Caelo    | Myrrh               | 25071404            | 1       |
| Caelo    | Myrrh               | Nachprüfung         | 1       |
| Caelo    | Myrrh               | 12244406            | 1       |
| Caelo    | Myrrh               | 11276806            | 3       |
| Caelo    | Myrrh               | 10057916            | 1       |
| Caelo    | Myrrh               | 14244602            | 1       |
| Caelo    | Myrrh               | 12269913            | 1       |
| Caelo    | Nettle leaf, cut    | 83142389            | 1       |
| Caelo    | Nettle leaf, cut    | nachprüfung         | 1       |
| Caelo    | Nettle leaf, cut    | 72085497            | 1       |
| Caelo    | Nettle leaf, cut    | 29071303            | 1       |
| Caelo    | Nettle leaf, cut    | intch:313011        | 1       |
| Caelo    | Nettle leaf, cut    | 7031302             | 1       |
| Caelo    | Nettle leaf, cut    | 10291411            | 3       |
| Caelo    | Nettle leaf, cut    | 613A-03054          | 1       |
| Caelo    | Nettle leaf, cut    | 33/AD1              | 1       |
| Caelo    | Nettle leaf, cut    | 10291410            | 2       |
| Caelo    | Nettle leaf, cut    | 2051302             | 1       |
| Caelo    | Nettle leaf, cut    | 83374109            | 1       |
| Caelo    | Nettle leaf, cut    | 3021401             | 1       |
| Caelo    | Nettle leaf, cut    |                     | 3       |
| Caelo    | Nettle leaf, cut    | 20111306            | 1       |
| Caelo    | Nettle leaf, cut    | 12183908-3391311070 | 1       |
| Caelo    | Nettle leaf, cut    | 18071202            | 1       |
| Caelo    | Nettle leaf, cut    | 1218707             | 1       |
| Caelo    | Nettle leaf, cut    | 12034402            | 4       |
| Caelo    | Nettle leaf, cut    | 12184706            | 5       |
| Caelo    | Nettle leaf, cut    | 12184503            | 3       |
| Caelo    | Nettle leaf, cut    | 12184502            | 2       |
| Caelo    | Nettle leaf, cut    | 12184005            | 8       |
| Caelo    | Nettle leaf, cut    | 12184004            | 10      |
| Caelo    | Nettle leaf, cut    | 12184001            | 6       |
| Caelo    | Nettle leaf, cut    | 12183914            | 12      |
| Caelo    | Nettle leaf, cut    | 12183911            | 16      |
| Caelo    | Nettle leaf, cut    | 12183910            | 12      |
| Caelo    | Nettle leaf, cut    | 12183909            | 1       |
| Caelo    | Nettle leaf, cut    | 12034403            | 9       |
| Caelo    | Nettle leaf, cut    | 12034414            | 1       |
| Caelo    | Nettle leaf, cut    | 120375901           | 1       |
| Caelo    | Nettle leaf, cut    | 12195101            | 4       |
| Caelo    | Nettle leaf, cut    | 10291422            | 4       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Nettle leaf, cut         | 12354001            | 1       |
| Caelo    | Nettle leaf, cut         | 12814001            | 1       |
| Caelo    | Nettle leaf, cut         | 17121205            | 1       |
| Caelo    | Nettle leaf, cut         | 10291414            | 5       |
| Caelo    | Nettle leaf, cut         | 10291413            | 2       |
| Caelo    | Nettle leaf, cut         | 10291409            | 1       |
| Caelo    | Nettle leaf, cut         | 10282807            | 2       |
| Caelo    | Nettle leaf, cut         | 10282806            | 1       |
| Caelo    | Nettle leaf, cut         | 10162712            | 1       |
| Caelo    | Nettle leaf, cut         | 19091205            | 1       |
| Caelo    | Nettle leaf, cut         | 15063105            | 1       |
| Caelo    | Nettle leaf, cut         | 12183908-3443311112 | 1       |
| Caelo    | Nettle leaf, cut         | 12183908-3405310181 | 1       |
| Caelo    | Nettle leaf, cut         | 14344903            | 1       |
| Caelo    | Nettle leaf, cut         | 13386801            | 6       |
| Caelo    | Nettle leaf, cut         | 13091302            | 1       |
| Caelo    | Nettle leaf, cut         | 12195001            | 1       |
| Caelo    | Nettle leaf, cut         | 1283910             | 1       |
| Caelo    | Nettle leaf, cut         | 14344907            | 4       |
| Caelo    | Nettle leaf, cut         | 12183908            | 6       |
| Caelo    | Nettle root, cut         | 10250203            | 1       |
| Caelo    | Nettle root, cut         | 6631B130610         | 1       |
| Caelo    | Nettle root, cut         | 11254902            | 5       |
| Caelo    | Nettle root, cut         | 11254903            | 5       |
| Caelo    | Nettle root, cut         | 11254904            | 3       |
| Caelo    | Nettle root, cut         | 6441A121024         | 1       |
| Caelo    | Nettle root, cut         | 11265002            | 6       |
| Caelo    | Nettle root, cut         | 10081202            | 1       |
| Caelo    | Nettle root, cut         | 11265003            | 2       |
| Caelo    | Nettle root, cut         | 11265006            | 1       |
| Caelo    | Nettle seed              | 13387109            | 1       |
| Caelo    | Nettle seed              | 16327001            | 1       |
| Caelo    | Nettle seed              | 15290602            | 1       |
| Caelo    | Nettle seed              | 20111301            | 1       |
| Caelo    | Nettle seed              | 13010612            | 2       |
| Caelo    | Nettle seed              | 13010607            | 1       |
| Caelo    | Nettle seed              | 12131505            | 1       |
| Caelo    | Nutmeg                   | 12376802            | 2       |
| Caelo    | Nutmeg                   | 12376805            | 1       |
| Caelo    | Nutmeg, powdered (spi... | 12102305            | 2       |
| Caelo    | Nutmeg, powdered (spi... | 12102306            | 1       |
| Caelo    | Nystatin                 | 12158004            | 1       |
| Caelo    | Nystatin                 | 13101201            | 1       |
| Caelo    | Nystatin                 | 11069716            | 1       |
| Caelo    | Nystatin                 | 11069706            | 2       |
| Caelo    | Nystatin                 | 11069704            | 1       |
| Caelo    | Nystatin                 | 6082013B            | 1       |
| Caelo    | Nystatin                 | 13173410            | 1       |
| Caelo    | Nystatin                 | 11069730            | 1       |
| Caelo    | Nystatin                 | 14363514            | 1       |
| Caelo    | Nystatin                 | 3101201             | 1       |
| Caelo    | Nystatin                 | 2091304             | 1       |
| Caelo    | Nystatin                 | 1/0913              | 2       |
| Caelo    | Nystatin                 | 15335313            | 1       |
| Caelo    | Nystatin                 | C129330             | 1       |
| Caelo    | Nystatin                 | 11069724            | 1       |
| Caelo    | Nystatin                 | 15335310            | 1       |
| Caelo    | Nystatin                 | 11069731            | 1       |
| Caelo    | Nystatin                 | 11069719            | 1       |
| Caelo    | Nystatin                 | 13173401            | 18      |

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| Supplier | Substance     | Batch               | Spectra |
|----------|---------------|---------------------|---------|
| Caelo    | Nystatin      | 12158021            | 7       |
| Caelo    | Nystatin      | 12158020            | 1       |
| Caelo    | Nystatin      | 12158019            | 5       |
| Caelo    | Nystatin      | 12158009            | 1       |
| Caelo    | Nystatin      | 12017003            | 1       |
| Caelo    | Nystatin      | 12158005            | 1       |
| Caelo    | Nystatin      | 12158004            | 4       |
| Caelo    | Nystatin      | 12158006            | 7       |
| Caelo    | Nystatin      | 120700902           | 1       |
| Caelo    | Nystatin      | 12017011            | 3       |
| Caelo    | Nystatin      | 12017010            | 2       |
| Caelo    | Nystatin      | 13101202            | 1       |
| Caelo    | Nystatin      | 12017009            | 1       |
| Caelo    | Nystatin      | 12017004            | 5       |
| Caelo    | Nystatin      | 12138021            | 2       |
| Caelo    | Nystatin      | 12017015            | 2       |
| Caelo    | Oak bark, cut | 11351201            | 3       |
| Caelo    | Oak bark, cut | 13360305            | 1       |
| Caelo    | Oak bark, cut | 11351209            | 11      |
| Caelo    | Oak bark, cut | 11351207-3384310110 | 1       |
| Caelo    | Oak bark, cut | 11351207            | 13      |
| Caelo    | Oak bark, cut | 11351206            | 14      |
| Caelo    | Oak bark, cut | 26081302            | 1       |
| Caelo    | Oak bark, cut | 1081401             | 1       |
| Caelo    | Oak bark, cut | 15146105            | 1       |
| Caelo    | Oak bark, cut | 15146109            | 2       |
| Caelo    | Oak bark, cut | 22081204            | 1       |
| Caelo    | Oak bark, cut | 19032013            | 2       |
| Caelo    | Oak bark, cut | 17101208            | 1       |
| Caelo    | Oak bark, cut | 15314901            | 1       |
| Caelo    | Oak bark, cut | 15314903            | 1       |
| Caelo    | Oak bark, cut | 15314904            | 1       |
| Caelo    | Oak bark, cut | 161212              | 1       |
| Caelo    | Oak bark, cut | 15314905            | 2       |
| Caelo    | Oak bark, cut | 280814A             | 1       |
| Caelo    | Oak bark, cut | 16081305            | 1       |
| Caelo    | Oak bark, cut | 3041301             | 1       |
| Caelo    | Oak bark, cut | 5091302             | 1       |
| Caelo    | Oak bark, cut | 15146105            | 5       |
| Caelo    | Oak bark, cut | 7021302             | 1       |
| Caelo    | Oak bark, cut | 10348605            | 1       |
| Caelo    | Oak bark, cut | 10348612            | 3       |
| Caelo    | Oak bark, cut | 10348613            | 2       |
| Caelo    | Oak bark, cut | 10348615            | 2       |
| Caelo    | Oak bark, cut | 11351202            | 5       |
| Caelo    | Oak bark, cut | 11351203            | 2       |
| Caelo    | Oak bark, cut | 11351205            | 4       |
| Caelo    | Oak bark, cut | 11351210            | 1       |
| Caelo    | Oak bark, cut | 12221101            | 13      |
| Caelo    | Oak bark, cut | 15146110            | 1       |
| Caelo    | Oak bark, cut | 15146102            | 1       |
| Caelo    | Oak bark, cut | 12221102            | 1       |
| Caelo    | Oak bark, cut | 12221104            | 3       |
| Caelo    | Oak bark, cut | 12221105            | 2       |
| Caelo    | Oak bark, cut | 10348606            | 1       |
| Caelo    | Oak bark, cut | 13360301            | 1       |
| Caelo    | Oak bark, cut | 15146104            | 1       |
| Caelo    | Oak bark, cut | 15146103            | 1       |
| Caelo    | Oak bark, cut | 10061504            | 1       |
| Caelo    | Oak bark, cut | 11351208            | 3       |

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| Supplier | Substance            | Batch       | Spectra |
|----------|----------------------|-------------|---------|
| Caelo    | Oak bark, cut        | 11351210    | 10      |
| Caelo    | Oak bark, cut        | 123test     | 1       |
| Caelo    | Oak bark, cut        | nachprüfung | 1       |
| Caelo    | Oak bark, cut        | 13360302    | 6       |
| Caelo    | Oak bark, cut        | 41109-4-P   | 1       |
| Caelo    | Oak bark, cut        | 15146104    | 3       |
| Caelo    | Oak bark, cut        | 13360306    | 2       |
| Caelo    | Oak bark, cut        | 13360306    | 1       |
| Caelo    | Oak bark, cut        | 26061206    | 1       |
| Caelo    | Oak bark, cut        | 13360304    | 1       |
| Caelo    | Oak bark, cut        | 14111316    | 1       |
| Caelo    | Oak bark, cut        | 13360309    | 2       |
| Caelo    | Oak bark, cut        | 13360311    | 2       |
| Caelo    | Oak bark, cut        | 13360312    | 5       |
| Caelo    | Oak bark, cut        | 15146102    | 1       |
| Caelo    | Oak bark, cut        | 14277004    | 1       |
| Caelo    | Oak bark, cut        | 14277004    | 2       |
| Caelo    | Oak bark, cut        | 14277004    | 1       |
| Caelo    | Oak bark, cut        | 15146101    | 2       |
| Caelo    | Oak bark, cut        | 15146101    | 1       |
| Caelo    | Oak bark, cut        | 13360308    | 1       |
| Caelo    | Oak bark, cut        | 2413M-01303 | 1       |
| Caelo    | Oak bark, powdered   | 10261513    | 1       |
| Caelo    | Oat straw, cut       | 11280017    | 2       |
| Caelo    | Oat straw, cut       | 11280008    | 3       |
| Caelo    | Oat straw, cut       | 11280015    | 3       |
| Caelo    | Oat straw, cut       | 11280014    | 1       |
| Caelo    | Oat straw, cut       | 11280012    | 2       |
| Caelo    | Oat straw, cut       | 11280010    | 1       |
| Caelo    | Oat straw, cut       | 11280011    | 1       |
| Caelo    | Oat straw, cut       | 11280019    | 1       |
| Caelo    | Oat straw, cut       | 11280006    | 2       |
| Caelo    | Olive leaf           | 12159803    | 1       |
| Caelo    | Olive leaf           | 12159805    | 1       |
| Caelo    | Oregano herb         | 11340708    | 1       |
| Caelo    | Oregano herb         | 11340709    | 1       |
| Caelo    | Oregano herb         | 12360904    | 1       |
| Caelo    | Oregano herb         | 12360901    | 6       |
| Caelo    | Oregano herb         | 11340703    | 2       |
| Caelo    | Oregano herb         | 12360902    | 2       |
| Caelo    | Oregano herb         | 11340705    | 2       |
| Caelo    | Orris root           | 1026706     | 1       |
| Caelo    | Orris root           | 13113404    | 1       |
| Caelo    | Orris root           | 13113401    | 2       |
| Caelo    | Orris root           | 13113402    | 1       |
| Caelo    | Orris root           | 11026704    | 5       |
| Caelo    | Orris root           | 11026701    | 2       |
| Caelo    | Orris root           | nachprüfung | 2       |
| Caelo    | Orris root           | 11026706    | 1       |
| Caelo    | Parsley herb, rubbed | 12376602    | 3       |
| Caelo    | Parsley herb, rubbed | 12376601    | 2       |
| Caelo    | Parsley herb, rubbed | 12376603    | 2       |
| Caelo    | Parsley herb, rubbed | 51978126    | 1       |
| Caelo    | Parsley root, cut    | 12080311    | 2       |
| Caelo    | Parsley root, cut    | 11038704    | 1       |
| Caelo    | Parsley root, cut    | nachprüfung | 1       |
| Caelo    | Parsley root, cut    | 13156003    | 1       |
| Caelo    | Parsley root, cut    | 13029403    | 1       |
| Caelo    | Parsley root, cut    | 12080309    | 1       |
| Caelo    | Parsley root, cut    | 13156005    | 1       |

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| <b>Supplier</b> | <b>Substance</b>        | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|-------------------------|---------------------|----------------|
| Caelo           | Parsley root, cut       | 12080302            | 1              |
| Caelo           | Parsley root, cut       | 11172103            | 1              |
| Caelo           | Parsley root, cut       | 11172101            | 1              |
| Caelo           | Parsley root, cut       | 12080304            | 1              |
| Caelo           | Passionflower herb, cut | 12031716            | 3              |
| Caelo           | Passionflower herb, cut | 2913A-01669         | 1              |
| Caelo           | Passionflower herb, cut | 15085105            | 1              |
| Caelo           | Passionflower herb, cut | 13141203            | 2              |
| Caelo           | Passionflower herb, cut | 13141202            | 7              |
| Caelo           | Passionflower herb, cut | 13141201            | 1              |
| Caelo           | Passionflower herb, cut | 12101301            | 1              |
| Caelo           | Passionflower herb, cut | 12031715            | 8              |
| Caelo           | Passionflower herb, cut | 11049113            | 1              |
| Caelo           | Passionflower herb, cut | 12031712            | 1              |
| Caelo           | Passionflower herb, cut | 12031713            | 1              |
| Caelo           | Passionflower herb, cut | 13141205            | 5              |
| Caelo           | Passionflower herb, cut | 12031717            | 7              |
| Caelo           | Passionflower herb, cut | 12031714            | 3              |
| Caelo           | Passionflower herb, cut | 1011A-01669         | 1              |
| Caelo           | Passionflower herb, cut | 110049112           | 1              |
| Caelo           | Passionflower herb, cut | 11049108            | 2              |
| Caelo           | Passionflower herb, cut | 11049111            | 1              |
| Caelo           | Passionflower herb, cut | 12031710            | 16             |
| Caelo           | Passionflower herb, cut | 11049114            | 1              |
| Caelo           | Passionflower herb, cut | 11049115            | 1              |
| Caelo           | Passionflower herb, cut | 11049116            | 4              |
| Caelo           | Passionflower herb, cut | 12031702            | 2              |
| Caelo           | Passionflower herb, cut | 12031703            | 2              |
| Caelo           | Passionflower herb, cut | 12031704            | 1              |
| Caelo           | Passionflower herb, cut | 12031705            | 5              |
| Caelo           | Passionflower herb, cut | 12031707            | 1              |
| Caelo           | Peppermint leaf, cut    | 20111215            | 1              |
| Caelo           | Peppermint leaf, cut    | 161212              | 1              |
| Caelo           | Peppermint leaf, cut    | 14339202            | 2              |
| Caelo           | Peppermint leaf, cut    | 14083102            | 3              |
| Caelo           | Peppermint leaf, cut    | 12266908            | 9              |
| Caelo           | Peppermint leaf, cut    | 12266911            | 1              |
| Caelo           | Peppermint leaf, cut    | 12266903            | 7              |
| Caelo           | Peppermint leaf, cut    | 12266904            | 3              |
| Caelo           | Peppermint leaf, cut    | 2181A1209-13        | 1              |
| Caelo           | Peppermint leaf, cut    | 12266912            | 1              |
| Caelo           | Peppermint leaf, cut    | 2181B090928         | 1              |
| Caelo           | Peppermint leaf, cut    | 13030805            | 6              |
| Caelo           | Peppermint leaf, cut    | 276514              | 4              |
| Caelo           | Peppermint leaf, cut    | Int.Ch.:313011      | 1              |
| Caelo           | Peppermint leaf, cut    | Nachprüfung         | 1              |
| Caelo           | Peppermint leaf, cut    | 20061202            | 1              |
| Caelo           | Peppermint leaf, cut    | 268320              | 1              |
| Caelo           | Peppermint leaf, cut    | 4912E-01503         | 1              |
| Caelo           | Peppermint leaf, cut    | 13030804            | 1              |
| Caelo           | Peppermint leaf, cut    | 13214707            | 2              |
| Caelo           | Peppermint leaf, cut    | 13214720            | 1              |
| Caelo           | Peppermint leaf, cut    | 13030806            | 1              |
| Caelo           | Peppermint leaf, cut    | 2181B140205         | 1              |
| Caelo           | Peppermint leaf, cut    | 11347609            | 1              |
| Caelo           | Peppermint leaf, cut    | 12054149            | 1              |
| Caelo           | Peppermint leaf, cut    | 1132803             | 1              |
| Caelo           | Peppermint leaf, cut    | 14221701            | 1              |
| Caelo           | Peppermint leaf, cut    | 12266908-343431160  | 1              |
| Caelo           | Peppermint leaf, cut    | 13030808-3401310161 | 1              |

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| Supplier | Substance                | Batch      | Spectra |
|----------|--------------------------|------------|---------|
| Caelo    | Peppermint leaf, cut     | 13214706   | 1       |
| Caelo    | Peppermint leaf, cut     | 13214705   | 1       |
| Caelo    | Peppermint leaf, cut     | 13105001   | 1       |
| Caelo    | Peppermint leaf, cut     | ChB:311092 | 1       |
| Caelo    | Peppermint leaf, cut     | 13030807   | 4       |
| Caelo    | Peppermint leaf, cut     | 313A-01503 | 1       |
| Caelo    | Peppermint leaf, cut     | 12032311   | 1       |
| Caelo    | Peppermint leaf, cut     | 12032319   | 2       |
| Caelo    | Peppermint leaf, cut     | 13030809   | 2       |
| Caelo    | Peppermint leaf, cut     | 13030808   | 1       |
| Caelo    | Peppermint leaf, cut     | 5091307    | 1       |
| Caelo    | Peppermint leaf, cut     | 11327808   | 5       |
| Caelo    | Peppermint leaf, cut     | 11327803   | 8       |
| Caelo    | Peppermint leaf, cut     | 11327802   | 1       |
| Caelo    | Peppermint leaf, cut     | 11327801   | 2       |
| Caelo    | Peppermint leaf, cut     | 12266913   | 10      |
| Caelo    | Peppermint leaf, cut     | 11294405   | 1       |
| Caelo    | Peppermint leaf, cut     | 11294401   | 3       |
| Caelo    | Peppermint leaf, cut     | 11294409   | 2       |
| Caelo    | Peppermint leaf, cut     | 6011403    | 1       |
| Caelo    | Peppermint leaf, cut     | 8101301    | 1       |
| Caelo    | Peppermint leaf, cut     | 912E-01505 | 1       |
| Caelo    | Phenobarbital            | 12D30-N02  | 1       |
| Caelo    | Phenol                   | 12223001   | 2       |
| Caelo    | Phenol                   | 11163802   | 1       |
| Caelo    | Phenol                   | 13296902   | 1       |
| Caelo    | Phenol                   | 11163801   | 1       |
| Caelo    | Phenol                   | 12223022   | 1       |
| Caelo    | Phenol                   | 12223020   | 1       |
| Caelo    | Phenol                   | 12223014   | 1       |
| Caelo    | Phenol                   | 12223005   | 1       |
| Caelo    | Phenol                   | 7061305    | 1       |
| Caelo    | Phenol                   | 11163809   | 1       |
| Caelo    | Piper cubeba             | 11081903   | 1       |
| Caelo    | Podophyllum resin (fr... | 12287805   | 1       |
| Caelo    | Podophyllum resin (fr... | 12287810   | 1       |
| Caelo    | Podophyllum resin (fr... | 11085807   | 6       |
| Caelo    | Podophyllum resin (fr... | 11085803   | 1       |
| Caelo    | Podophyllum resin (fr... | 11085811   | 1       |
| Caelo    | Podophyllum resin (fr... | 12379903   | 1       |
| Caelo    | Podophyllum resin (fr... | 82433349   | 1       |
| Caelo    | Potassium hydrocarbon... | 13141926   | 1       |
| Caelo    | Potassium hydrocarbon... | 20080410-3 | 1       |
| Caelo    | Potassium hydrocarbon... | 11105801   | 1       |
| Caelo    | Potassium hydrocarbon... | 11105804   | 2       |
| Caelo    | Potassium hydrocarbon... | 12141920   | 1       |
| Caelo    | Potassium hydrocarbon... | 12141912   | 3       |
| Caelo    | Potassium hydrocarbon... | 13390303   | 1       |
| Caelo    | Potassium hydrocarbon... | 12141910   | 13      |
| Caelo    | Potassium hydrocarbon... | 13390307   | 1       |
| Caelo    | Potassium hydrocarbon... | 12239705   | 1       |
| Caelo    | Potassium hydrocarbon... | 11105812   | 2       |
| Caelo    | Potassium hydrocarbon... | 12239703   | 8       |
| Caelo    | Potassium hydrocarbon... | 12239702   | 2       |
| Caelo    | Potassium hydrocarbon... | 11105808   | 1       |
| Caelo    | Potassium hydrocarbon... | 12141905   | 3       |
| Caelo    | Potassium hydrocarbon... | 11105818   | 2       |
| Caelo    | Potassium hydrocarbon... | 12141919   | 3       |
| Caelo    | Potassium hydrocarbon... | 12239701   | 5       |
| Caelo    | Potassium hydrocarbon... | 1214190    | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|--------------------------|---------------------|----------------|
| Caelo           | Potassium hydrocarbon... | 24051301            | 1              |
| Caelo           | Potassium hydrocarbon... | 12230703            | 1              |
| Caelo           | Potassium hydrocarbon... | 6011405             | 1              |
| Caelo           | Potassium hydrocarbon... | 1214924             | 1              |
| Caelo           | Potassium hydrocarbon... | 12141930            | 2              |
| Caelo           | Potassium hydrocarbon... | 8101202             | 1              |
| Caelo           | Potassium hydrocarbon... | 11105822            | 1              |
| Caelo           | Potassium hydrocarbon... | 1011M-01728         | 1              |
| Caelo           | Potassium hydrocarbon... | 10052610            | 2              |
| Caelo           | Potassium hydrocarbon... | 10052629            | 1              |
| Caelo           | Potassium hydrocarbon... | 3812Q-01728         | 1              |
| Caelo           | Potassium hydrocarbon... | 700544              | 1              |
| Caelo           | Potassium hydrocarbon... | IntCh:217002        | 1              |
| Caelo           | Potassium hydrocarbon... | 33131-01728         | 1              |
| Caelo           | Potassium hydrocarbon... | 12141924            | 3              |
| Caelo           | Potassium hydrocarbon... | 10052622            | 1              |
| Caelo           | Potassium hydroxide      | 12382601            | 2              |
| Caelo           | Potassium hydroxide      | 17091202            | 1              |
| Caelo           | Potassium hydroxide      | 27111310            | 1              |
| Caelo           | Potassium hydroxide      | 12382611            | 2              |
| Caelo           | Potassium hydroxide      | 13275207            | 1              |
| Caelo           | Potassium hydroxide      | 12057908            | 2              |
| Caelo           | Potassium hydroxide      | 12057906            | 1              |
| Caelo           | Potassium hydroxide      | 12382603            | 6              |
| Caelo           | Potassium hydroxide      | 12382606            | 2              |
| Caelo           | Potassium hydroxide      | 12057903            | 1              |
| Caelo           | Potassium hydroxide      | 12057912            | 2              |
| Caelo           | Potassium hydroxide      | 13275201            | 1              |
| Caelo           | Potassium hydroxide      | 12057905            | 2              |
| Caelo           | Potassium hydroxide      | 11165705            | 1              |
| Caelo           | Primrose flower          | 13086603            | 5              |
| Caelo           | Primrose flower          | 11206808            | 2              |
| Caelo           | Primrose flower          | 11206807            | 1              |
| Caelo           | Primrose flower          | 11206805            | 1              |
| Caelo           | Primrose flower          | 11206804            | 1              |
| Caelo           | Primrose flower          | 10072509            | 1              |
| Caelo           | Primrose flower          | 13276904            | 1              |
| Caelo           | Primrose flower          | 11206803            | 5              |
| Caelo           | Primrose flower          | 13086605            | 1              |
| Caelo           | Primrose flower          | 11374402            | 1              |
| Caelo           | Primrose flower          | 11268005            | 2              |
| Caelo           | Primrose flower          | 25091306            | 1              |
| Caelo           | Primrose flower          | 13086608            | 1              |
| Caelo           | Primrose flower          | 10207104            | 1              |
| Caelo           | Primrose flower          | 9021301             | 1              |
| Caelo           | Primrose flower          | 5021303             | 1              |
| Caelo           | Primrose flower          | 11206603            | 1              |
| Caelo           | Primrose flower          | 11374401            | 12             |
| Caelo           | Primrose flower          | 1308660             | 1              |
| Caelo           | Primrose flower          | 11206810            | 7              |
| Caelo           | Primrose flower          | 13086603            | 2              |
| Caelo           | Primrose flower          | 11374404            | 1              |
| Caelo           | Primrose flower          | 113744044           | 1              |
| Caelo           | Primrose flower          | 13086602            | 2              |
| Caelo           | Primrose flower          | 11374403            | 1              |
| Caelo           | Primrose flower          | 11206811            | 1              |
| Caelo           | Primrose flower          | 11206811            | 4              |
| Caelo           | Primrose root, cut       | 212Q-02159          | 1              |
| Caelo           | Primrose root, cut       | 12064502            | 1              |
| Caelo           | Primrose root, cut       | 13087005-3534411072 | 1              |

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| Supplier | Substance                | Batch         | Spectra |
|----------|--------------------------|---------------|---------|
| Caelo    | Primrose root, cut       | 10382013      | 2       |
| Caelo    | Primrose root, cut       | 24011301      | 1       |
| Caelo    | Primrose root, cut       | 4021410       | 1       |
| Caelo    | Primrose root, cut       | 10382012      | 1       |
| Caelo    | Primrose root, cut       | 13087002      | 7       |
| Caelo    | Primrose root, cut       | 12064503      | 1       |
| Caelo    | Primrose root, cut       | 13087004      | 1       |
| Caelo    | Primrose root, cut       | 10382010      | 1       |
| Caelo    | Primrose root, cut       | 13067001      | 1       |
| Caelo    | Primrose root, cut       | Int.Ch:318090 | 1       |
| Caelo    | Primrose root, cut       | 71653517      | 1       |
| Caelo    | Primrose root, cut       | 5010E-02159   | 1       |
| Caelo    | Primrose root, cut       | 13087005      | 3       |
| Caelo    | Primrose root, cut       | 10382009      | 2       |
| Caelo    | Primrose root, cut       | 12064506      | 4       |
| Caelo    | Primrose root, cut       | 13087001      | 1       |
| Caelo    | Propolis extract (96%... | 11124101      | 1       |
| Caelo    | Psyllium seed            | 13305907      | 5       |
| Caelo    | Psyllium seed            | 12185503      | 3       |
| Caelo    | Psyllium seed            | 12185502      | 1       |
| Caelo    | Psyllium seed            | 12140301      | 7       |
| Caelo    | Psyllium seed            | 15190303      | 4       |
| Caelo    | Psyllium seed            | 7380a120911   | 1       |
| Caelo    | Psyllium seed            | 15190304      | 3       |
| Caelo    | Psyllium seed            | 15190306      | 2       |
| Caelo    | Psyllium seed            | 12185508      | 3       |
| Caelo    | Psyllium seed            | 12185504      | 11      |
| Caelo    | Psyllium seed            | 15249313      | 2       |
| Caelo    | Psyllium seed            | 13305911      | 1       |
| Caelo    | Psyllium seed            | 13305903      | 1       |
| Caelo    | Psyllium seed            | 13305906      | 2       |
| Caelo    | Psyllium seed            | 12185509      | 6       |
| Caelo    | Psyllium seed            | 12276510      | 1       |
| Caelo    | Psyllium seed            | 13305908      | 3       |
| Caelo    | Psyllium seed            | 15190302      | 3       |
| Caelo    | Psyllium seed            | 13234309      | 1       |
| Caelo    | Psyllium seed            | 13234310      | 3       |
| Caelo    | Psyllium seed            | 13305910      | 4       |
| Caelo    | Psyllium seed            | 13305904      | 2       |
| Caelo    | Psyllium seed            | 10291204      | 1       |
| Caelo    | Psyllium seed            | 10061503      | 1       |
| Caelo    | Psyllium seed            | 9336709       | 1       |
| Caelo    | Psyllium seed            | 11185811      | 4       |
| Caelo    | Psyllium seed            | 11185803      | 1       |
| Caelo    | Psyllium seed            | 10291207      | 7       |
| Caelo    | Psyllium seed            | 10291205      | 1       |
| Caelo    | Psyllium seed            | 10291206      | 1       |
| Caelo    | Pumpkin seed, peeled     | 12249011      | 2       |
| Caelo    | Pumpkin seed, peeled     | 12249001      | 2       |
| Caelo    | Pumpkin seed, peeled     | 122490911     | 1       |
| Caelo    | Pumpkin seed, peeled     | 14073603      | 1       |
| Caelo    | Pumpkin seed, peeled     | 140736306     | 1       |
| Caelo    | Ramsons herb, cut        | 11182203      | 1       |
| Caelo    | Ramsons herb, cut        | 14343305      | 1       |
| Caelo    | Ramsons herb, cut        | 12380802      | 2       |
| Caelo    | Ramsons herb, cut        | 3511B111005   | 2       |
| Caelo    | Ramsons herb, cut        | 12380803      | 2       |
| Caelo    | Ramsons herb, cut        | 11182205      | 1       |
| Caelo    | Ramsons herb, cut        | 11182204      | 1       |
| Caelo    | Ramsons herb, cut        | 12380801      | 2       |

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| <b>Supplier</b> | <b>Substance</b>    | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|---------------------|---------------------|----------------|
| Caelo           | Raspberry leaf, cut | 11030707            | 3              |
| Caelo           | Raspberry leaf, cut | 12362708            | 3              |
| Caelo           | Raspberry leaf, cut | 1210315             | 1              |
| Caelo           | Raspberry leaf, cut | 12362706            | 33             |
| Caelo           | Raspberry leaf, cut | 12103109            | 2              |
| Caelo           | Raspberry leaf, cut | 12103108            | 10             |
| Caelo           | Raspberry leaf, cut | 12362710            | 13             |
| Caelo           | Raspberry leaf, cut | 12103102            | 2              |
| Caelo           | Raspberry leaf, cut | 12362705            | 10             |
| Caelo           | Raspberry leaf, cut | 11071301            | 1              |
| Caelo           | Raspberry leaf, cut | 12362704            | 5              |
| Caelo           | Raspberry leaf, cut | 12362702            | 8              |
| Caelo           | Raspberry leaf, cut | 12103111            | 21             |
| Caelo           | Raspberry leaf, cut | 12103107            | 12             |
| Caelo           | Raspberry leaf, cut | 11121201            | 1              |
| Caelo           | Raspberry leaf, cut | 12130107            | 1              |
| Caelo           | Raspberry leaf, cut | 18101203            | 1              |
| Caelo           | Raspberry leaf, cut | 13086704            | 1              |
| Caelo           | Raspberry leaf, cut | 1310603             | 1              |
| Caelo           | Raspberry leaf, cut | 13101803            | 1              |
| Caelo           | Raspberry leaf, cut | 13101603            | 6              |
| Caelo           | Raspberry leaf, cut | 30011408            | 1              |
| Caelo           | Raspberry leaf, cut | 2909211511          | 1              |
| Caelo           | Raspberry leaf, cut | 25091201            | 1              |
| Caelo           | Raspberry leaf, cut | 22081201            | 1              |
| Caelo           | Raspberry leaf, cut | 21051302            | 1              |
| Caelo           | Raspberry leaf, cut | 20081311            | 1              |
| Caelo           | Raspberry leaf, cut | 10013410            | 1              |
| Caelo           | Raspberry leaf, cut | 18041304            | 1              |
| Caelo           | Raspberry leaf, cut | 13038003            | 3              |
| Caelo           | Raspberry leaf, cut | 17121203            | 1              |
| Caelo           | Raspberry leaf, cut | 14018803            | 1              |
| Caelo           | Raspberry leaf, cut | 13086706            | 1              |
| Caelo           | Raspberry leaf, cut | 13038002            | 1              |
| Caelo           | Raspberry leaf, cut | 9101204             | 1              |
| Caelo           | Raspberry leaf, cut | 11030706            | 4              |
| Caelo           | Raspberry leaf, cut | 9011404             | 1              |
| Caelo           | Raspberry leaf, cut | 12362709            | 5              |
| Caelo           | Raspberry leaf, cut | 12362707            | 6              |
| Caelo           | Raspberry leaf, cut | 12362703            | 10             |
| Caelo           | Raspberry leaf, cut | 12362701            | 7              |
| Caelo           | Raspberry leaf, cut | 10013409            | 2              |
| Caelo           | Raspberry leaf, cut | 613M-01511          | 1              |
| Caelo           | Raspberry leaf, cut | 1236705             | 1              |
| Caelo           | Raspberry leaf, cut | 314U1511            | 1              |
| Caelo           | Raspberry leaf, cut | 12103105            | 18             |
| Caelo           | Raspberry leaf, cut | 13101605            | 1              |
| Caelo           | Raspberry leaf, cut | 13101602-347312141  | 1              |
| Caelo           | Raspberry leaf, cut | 12362710-3432311160 | 1              |
| Caelo           | Raspberry leaf, cut | 11030705            | 1              |
| Caelo           | Raspberry leaf, cut | 13127901            | 3              |
| Caelo           | Raspberry leaf, cut | 12362711            | 10             |
| Caelo           | Raspberry leaf, cut | 9081205             | 1              |
| Caelo           | Raspberry leaf, cut | 12368706            | 1              |
| Caelo           | Raspberry leaf, cut | 231013c             | 1              |
| Caelo           | Raspberry leaf, cut | 8031307             | 1              |
| Caelo           | Raspberry leaf, cut | 713E-01511          | 1              |
| Caelo           | Raspberry leaf, cut | 7011402             | 1              |
| Caelo           | Raspberry leaf, cut | 6859427             | 1              |
| Caelo           | Raspberry leaf, cut | 2405211511          | 1              |

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| Supplier | Substance             | Batch               | Spectra |
|----------|-----------------------|---------------------|---------|
| Caelo    | Raspberry leaf, cut   | 23051204            | 1       |
| Caelo    | Raspberry leaf, cut   | 12392709            | 1       |
| Caelo    | Raspberry leaf, cut   | 10013407            | 1       |
| Caelo    | Raspberry leaf, cut   | 11030704            | 2       |
| Caelo    | Raspberry leaf, cut   | 4071202             | 1       |
| Caelo    | Raspberry leaf, cut   | 10136412            | 1       |
| Caelo    | Raspberry leaf, cut   | 307211511           | 1       |
| Caelo    | Raspberry leaf, cut   | 10136404            | 1       |
| Caelo    | Raspberry leaf, cut   | IntCh:311090        | 1       |
| Caelo    | Raspberry leaf, cut   | 10013406            | 4       |
| Caelo    | Raspberry leaf, cut   | 261490              | 1       |
| Caelo    | Red poppy petals, cut | 12330205            | 1       |
| Caelo    | Red-rose petal        | 12380004            | 1       |
| Caelo    | Red-rose petal        | 12380008            | 2       |
| Caelo    | Red-rose petal        | 13126304            | 1       |
| Caelo    | Red-rose petal, cut   | 12380004            | 2       |
| Caelo    | Red-rose petal, cut   | 11304904            | 5       |
| Caelo    | Red-rose petal, cut   | 11304901            | 3       |
| Caelo    | Red-rose petal, cut   | 11011301            | 1       |
| Caelo    | Red-rose petal, cut   | 10306514            | 1       |
| Caelo    | Red-rose petal, cut   | 10113211            | 1       |
| Caelo    | Red-rose petal, cut   | 13194402            | 1       |
| Caelo    | Red-rose petal, cut   | 11304910            | 1       |
| Caelo    | Red-rose petal, cut   | 11304912            | 2       |
| Caelo    | Red-rose petal, cut   | 12380001            | 5       |
| Caelo    | Red-rose petal, cut   | 13194403            | 4       |
| Caelo    | Red-rose petal, cut   | 12380008            | 1       |
| Caelo    | Red-rose petal, cut   | 1319002             | 1       |
| Caelo    | Red-rose petal, cut   | 11304906            | 3       |
| Caelo    | Red-rose petal, cut   | 11304908            | 1       |
| Caelo    | Red-rose petal, cut   | 12380007-3357319071 | 1       |
| Caelo    | Redwood               | 12041403            | 1       |
| Caelo    | Redwood               | 12049608            | 2       |
| Caelo    | Redwood               | 13106901            | 1       |
| Caelo    | Redwood               | 12049607            | 2       |
| Caelo    | Restharrow root, cut  | 11103107            | 2       |
| Caelo    | Restharrow root, cut  | 1230004             | 1       |
| Caelo    | Restharrow root, cut  | 12330001            | 13      |
| Caelo    | Restharrow root, cut  | Int.Ch:212150       | 1       |
| Caelo    | Restharrow root, cut  | 12330002            | 1       |
| Caelo    | Restharrow root, cut  | 72439069            | 1       |
| Caelo    | Restharrow root, cut  | 11103105            | 2       |
| Caelo    | Restharrow root, cut  | 71035467            | 1       |
| Caelo    | Restharrow root, cut  | 12330005            | 5       |
| Caelo    | Restharrow root, cut  | 12330001            | 1       |
| Caelo    | Restharrow root, cut  | 21011306            | 1       |
| Caelo    | Restharrow root, cut  | 20111213            | 1       |
| Caelo    | Restharrow root, cut  | 12330003            | 2       |
| Caelo    | Restharrow root, cut  | 6101201             | 1       |
| Caelo    | Restharrow root, cut  | 4021406             | 1       |
| Caelo    | Restharrow root, cut  | 11247302            | 2       |
| Caelo    | Restharrow root, cut  | 15101313            | 1       |
| Caelo    | Rhubarb, cut          | 1811a-02187         | 1       |
| Caelo    | Rhubarb, cut          | 11057815            | 1       |
| Caelo    | Rhubarb, cut          | 25111305            | 1       |
| Caelo    | Rhubarb, cut          | 4612A-02187         | 1       |
| Caelo    | Rhubarb, cut          | 12211903            | 4       |
| Caelo    | Rhubarb, cut          | 11057810            | 2       |
| Caelo    | Rhubarb, cut          | 12211902            | 5       |
| Caelo    | Rhubarb, cut          | 11057809            | 1       |

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| <b>Supplier</b> | <b>Substance</b>      | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|-----------------------|---------------------|----------------|
| Caelo           | Rhubarb, cut          | 12211901            | 1              |
| Caelo           | Rhubarb, cut          | 11057804            | 1              |
| Caelo           | Rhubarb, cut          | 12211906            | 1              |
| Caelo           | Rhubarb, cut          | 14155404            | 1              |
| Caelo           | Rhubarb, cut          | 13235205            | 1              |
| Caelo           | Rhubarb, cut          | 13235203            | 2              |
| Caelo           | Rhubarb, cut          | 10071302            | 1              |
| Caelo           | Rhubarb, cut          | 11321806            | 1              |
| Caelo           | Rhubarb, cut          | 13235201            | 2              |
| Caelo           | Rhubarb, cut          | 11057812            | 1              |
| Caelo           | Rhubarb, cut          | 11057818            | 3              |
| Caelo           | Rhubarb, cut          | 15101301            | 1              |
| Caelo           | Rhubarb, cut          | 12211910            | 1              |
| Caelo           | Rhubarb, cut          | 12211908            | 2              |
| Caelo           | Rhubarb, cut          | 12211904            | 2              |
| Caelo           | Rhubarb, cut          | 11057811            | 1              |
| Caelo           | Rhubarb, cut          | 11265902            | 1              |
| Caelo           | Rhubarb, powdered     | 13193104            | 4              |
| Caelo           | Rhubarb, powdered     | 11043809            | 1              |
| Caelo           | Rhubarb, powdered     | 11043818            | 1              |
| Caelo           | Rhubarb, powdered     | 9071201             | 1              |
| Caelo           | Rhubarb, powdered     | 11043819            | 2              |
| Caelo           | Rhubarb, powdered     | 11043816            | 1              |
| Caelo           | Rhubarb, powdered     | 11043816            | 2              |
| Caelo           | Rhubarb, powdered     | 23061402            | 1              |
| Caelo           | Rhubarb, powdered     | 11043817            | 1              |
| Caelo           | Rhubarb, powdered     | 11043825            | 2              |
| Caelo           | Rhubarb, powdered     | 13193109            | 1              |
| Caelo           | Rhubarb, powdered     | 11043818            | 1              |
| Caelo           | Rhubarb, powdered     | 13193106            | 2              |
| Caelo           | Rhubarb, powdered     | 11043826            | 1              |
| Caelo           | Rhubarb, powdered     | 11043822            | 1              |
| Caelo           | Ribwort plantain, cut | 13410612            | 1              |
| Caelo           | Ribwort plantain, cut | 1362903             | 1              |
| Caelo           | Ribwort plantain, cut | 25091305            | 1              |
| Caelo           | Ribwort plantain, cut | 12362903-3388311070 | 1              |
| Caelo           | Ribwort plantain, cut | 25041301            | 1              |
| Caelo           | Ribwort plantain, cut | 12362903            | 42             |
| Caelo           | Ribwort plantain, cut | 13410611            | 1              |
| Caelo           | Ribwort plantain, cut | 15096301            | 1              |
| Caelo           | Ribwort plantain, cut | 14199202            | 1              |
| Caelo           | Ribwort plantain, cut | 23121304            | 1              |
| Caelo           | Ribwort plantain, cut | 13113001            | 8              |
| Caelo           | Ribwort plantain, cut | 22021302            | 1              |
| Caelo           | Ribwort plantain, cut | 20111304            | 1              |
| Caelo           | Ribwort plantain, cut | 15096307            | 1              |
| Caelo           | Ribwort plantain, cut | 15096308            | 1              |
| Caelo           | Ribwort plantain, cut | 15101204            | 1              |
| Caelo           | Ribwort plantain, cut | 20111208            | 1              |
| Caelo           | Ribwort plantain, cut | 19121202            | 1              |
| Caelo           | Ribwort plantain, cut | 15111302            | 1              |
| Caelo           | Ribwort plantain, cut | 17071201            | 1              |
| Caelo           | Ribwort plantain, cut | 16101304            | 1              |
| Caelo           | Ribwort plantain, cut | 25021303            | 1              |
| Caelo           | Ribwort plantain, cut | 13113004            | 18             |
| Caelo           | Ribwort plantain, cut | 13232401            | 1              |
| Caelo           | Ribwort plantain, cut | 13410603            | 4              |
| Caelo           | Ribwort plantain, cut | 12225801            | 1              |
| Caelo           | Ribwort plantain, cut | 12225803            | 3              |
| Caelo           | Ribwort plantain, cut | 31051316            | 1              |

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| Supplier | Substance             | Batch               | Spectra |
|----------|-----------------------|---------------------|---------|
| Caelo    | Ribwort plantain, cut | 28061301            | 1       |
| Caelo    | Ribwort plantain, cut | 12225804            | 1       |
| Caelo    | Ribwort plantain, cut | 12362906            | 9       |
| Caelo    | Ribwort plantain, cut | 13113006            | 5       |
| Caelo    | Ribwort plantain, cut | 11061304            | 1       |
| Caelo    | Ribwort plantain, cut | 13113007            | 9       |
| Caelo    | Ribwort plantain, cut | 12362901            | 2       |
| Caelo    | Ribwort plantain, cut | 4271A100615G        | 1       |
| Caelo    | Ribwort plantain, cut | 13113008            | 5       |
| Caelo    | Ribwort plantain, cut | 10315715            | 9       |
| Caelo    | Ribwort plantain, cut | 12225802            | 7       |
| Caelo    | Ribwort plantain, cut | 1021309             | 1       |
| Caelo    | Ribwort plantain, cut | 10315711            | 5       |
| Caelo    | Ribwort plantain, cut | 13113010            | 4       |
| Caelo    | Ribwort plantain, cut | 15321102            | 1       |
| Caelo    | Ribwort plantain, cut | 13113005            | 5       |
| Caelo    | Ribwort plantain, cut | 10315705            | 2       |
| Caelo    | Ribwort plantain, cut | 10011402            | 1       |
| Caelo    | Ribwort plantain, cut | 8061208             | 1       |
| Caelo    | Ribwort plantain, cut | 6111209             | 1       |
| Caelo    | Ribwort plantain, cut | 4021411             | 1       |
| Caelo    | Ribwort plantain, cut | 10315714            | 3       |
| Caelo    | Ribwort plantain, cut | 2031302             | 1       |
| Caelo    | Ribwort plantain, cut | 1313007             | 1       |
| Caelo    | Ribwort plantain, cut | 1213E-03556         | 1       |
| Caelo    | Ribwort plantain, cut | 13410601            | 1       |
| Caelo    | Ribwort plantain, cut | 13113004-3488312172 | 1       |
| Caelo    | Ribwort plantain, cut | 10328702            | 2       |
| Caelo    | Ribwort plantain, cut | 12362902            | 6       |
| Caelo    | Robert herb, cut      | 12319305            | 1       |
| Caelo    | Robert herb, cut      | 11147804            | 1       |
| Caelo    | Robert herb, cut      | 11147812            | 3       |
| Caelo    | Robert herb, cut      | 12319301            | 1       |
| Caelo    | Robert herb, cut      | 12319302            | 2       |
| Caelo    | Robert herb, cut      | 11147807            | 5       |
| Caelo    | Robert herb, cut      | 8121203             | 1       |
| Caelo    | Robert herb, cut      | 12319304            | 2       |
| Caelo    | Robert herb, cut      | 11147810            | 4       |
| Caelo    | Rose hips peel, cut   | 2851A120904konv.    | 1       |
| Caelo    | Rose hips peel, cut   | 29131-01543         | 1       |
| Caelo    | Rose hips peel, cut   | 12288302            | 7       |
| Caelo    | Rose hips peel, cut   | 1021305             | 1       |
| Caelo    | Rose hips peel, cut   | 11301407            | 12      |
| Caelo    | Rose hips peel, cut   | 10157309            | 1       |
| Caelo    | Rose hips peel, cut   | 10157312            | 2       |
| Caelo    | Rose hips peel, cut   | 15061210            | 1       |
| Caelo    | Rose hips peel, cut   | 25061203            | 1       |
| Caelo    | Rose hips peel, cut   | 14050705            | 1       |
| Caelo    | Rose hips peel, cut   | 14050704            | 1       |
| Caelo    | Rose hips peel, cut   | 5091301             | 1       |
| Caelo    | Rose hips peel, cut   | 12064207            | 1       |
| Caelo    | Rose hips peel, cut   | 13317805            | 1       |
| Caelo    | Rose hips peel, cut   | 11301403            | 3       |
| Caelo    | Rose hips peel, cut   | 13317801            | 2       |
| Caelo    | Rose hips peel, cut   | 12357504            | 2       |
| Caelo    | Rose hips peel, cut   | 11301404            | 1       |
| Caelo    | Rose hips peel, cut   | 11301401            | 2       |
| Caelo    | Rose hips peel, cut   | 12357502            | 4       |
| Caelo    | Rose hips peel, cut   | 12357505            | 11      |
| Caelo    | Rose hips peel, cut   | 9121301             | 1       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Rose hips peel, cut      | 11301405            | 2       |
| Caelo    | Rose hips peel, cut      | 7031305             | 1       |
| Caelo    | Rose hips peel, cut      | 12357501            | 1       |
| Caelo    | Rose hips peel, cut      | 12288301            | 1       |
| Caelo    | Rose hips peel, cut      | 10101206            | 1       |
| Caelo    | Rose hips with peel, ... | 16111201            | 1       |
| Caelo    | Rose hips with peel, ... | nachprüfung         | 2       |
| Caelo    | Rose hips with peel, ... | 12064207            | 4       |
| Caelo    | Rose hips with peel, ... | 19111204            | 1       |
| Caelo    | Rose hips with peel, ... | 13048704            | 3       |
| Caelo    | Rose hips with peel, ... | 12064213            | 1       |
| Caelo    | Rose hips with peel, ... | 13048701            | 2       |
| Caelo    | Rose hips with peel, ... | 12064212            | 2       |
| Caelo    | Rose hips with peel, ... | 12064201            | 1       |
| Caelo    | Rose hips with peel, ... | 13048703            | 1       |
| Caelo    | Rose hips with peel, ... | 13048704            | 2       |
| Caelo    | Rose hips with peel, ... | 13097405            | 1       |
| Caelo    | Rose hips with peel, ... | 1512211542          | 1       |
| Caelo    | Rose hips with peel, ... | 2103311542          | 1       |
| Caelo    | Rose hips with peel, ... | 2402211542          | 1       |
| Caelo    | Rose hips with peel, ... | 307211542           | 1       |
| Caelo    | Rose hips with peel, ... | 12064206            | 1       |
| Caelo    | Rose hips with peel, ... | 12064213            | 1       |
| Caelo    | Rose hips with peel, ... | 12064212            | 4       |
| Caelo    | Rose hips with peel, ... | 13048703            | 1       |
| Caelo    | Rose hips with peel, ... | 12064202            | 2       |
| Caelo    | Rose hips with peel, ... | 12064209            | 4       |
| Caelo    | Rose hips with peel, ... | 12029004            | 1       |
| Caelo    | Rose hips with peel, ... | 12029011            | 1       |
| Caelo    | Rose hips with peel, ... | 12064210            | 3       |
| Caelo    | Rose hips with peel, ... | 12029008            | 1       |
| Caelo    | Rose hips with peel, ... | 12064207            | 2       |
| Caelo    | Rose hips with peel, ... | 114Q-01542          | 1       |
| Caelo    | Rose hips with peel, ... | 12064210            | 1       |
| Caelo    | Rose hips with peel, ... | 12064209            | 1       |
| Caelo    | Rose hips with peel, ... | 12064202            | 2       |
| Caelo    | Rose hips with peel, ... | 12064206            | 1       |
| Caelo    | Rose mallow flower, cut  | 13040402            | 2       |
| Caelo    | Rose mallow flower, cut  | 13040401            | 3       |
| Caelo    | Rose mallow flower, cut  | 10244507            | 1       |
| Caelo    | Rose mallow flower, cut  | 9267604             | 1       |
| Caelo    | Roselle                  | 12267507            | 2       |
| Caelo    | Roselle                  | 11036503            | 1       |
| Caelo    | Roselle                  | 11036511            | 1       |
| Caelo    | Roselle                  | 12007303            | 1       |
| Caelo    | Roselle                  | 12007306            | 1       |
| Caelo    | Roselle                  | 12267504-3428311150 | 1       |
| Caelo    | Roselle                  | 12267502            | 3       |
| Caelo    | Roselle                  | 12267504            | 1       |
| Caelo    | Roselle                  | 5212U-01460         | 1       |
| Caelo    | Roselle                  | 12267504            | 3       |
| Caelo    | Roselle                  | 11036501            | 1       |
| Caelo    | Roselle                  | 11036504            | 1       |
| Caelo    | Roselle                  | 11036509            | 1       |
| Caelo    | Roselle                  | 11036512            | 1       |
| Caelo    | Roselle                  | 12267501            | 3       |
| Caelo    | Roselle                  | 12267502            | 4       |
| Caelo    | Roselle                  | 12267503            | 2       |
| Caelo    | Roselle                  | 13010204            | 1       |
| Caelo    | Roselle                  | 7121301             | 1       |

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| Supplier | Substance          | Batch         | Spectra |
|----------|--------------------|---------------|---------|
| Caelo    | Rosemary leaf, cut | 1415901       | 1       |
| Caelo    | Rosemary leaf, cut | 11193406      | 1       |
| Caelo    | Rosemary leaf, cut | 11193407      | 1       |
| Caelo    | Rosemary leaf, cut | 12225902      | 1       |
| Caelo    | Rosemary leaf, cut | 13128801      | 1       |
| Caelo    | Rosemary leaf, cut | 13128802      | 2       |
| Caelo    | Rosemary leaf, cut | 13128805      | 1       |
| Caelo    | Rosemary leaf, cut | 28051404      | 1       |
| Caelo    | Rosemary leaf, cut | 11193405      | 1       |
| Caelo    | Rosemary leaf, cut | 11193408      | 6       |
| Caelo    | Rosemary leaf, cut | 14082902      | 1       |
| Caelo    | Rosemary leaf, cut | 14159602      | 1       |
| Caelo    | Rosemary leaf, cut | 1812A-01510   | 1       |
| Caelo    | Rosemary leaf, cut | IntCh: 313060 | 1       |
| Caelo    | Rosemary leaf, cut | 14082901      | 1       |
| Caelo    | Rosemary leaf, cut | 11193404      | 2       |
| Caelo    | Rosemary leaf, cut | 11192408      | 1       |
| Caelo    | Rosemary leaf, cut | 11193405      | 3       |
| Caelo    | Rosemary leaf, cut | 5041302       | 1       |
| Caelo    | Rosemary leaf, cut | 13128806      | 3       |
| Caelo    | Rosemary leaf, cut | 11193403      | 1       |
| Caelo    | Rosemary leaf, cut | 11193402      | 3       |
| Caelo    | Rosemary leaf, cut | 14159601      | 1       |
| Caelo    | Rosemary leaf, cut | 15125001      | 3       |
| Caelo    | Rosemary leaf, cut | 15125008      | 1       |
| Caelo    | Rosemary leaf, cut | 10139811      | 1       |
| Caelo    | Rue herb, cut      | 9336802       | 1       |
| Caelo    | Rue herb, cut      | 11371803      | 1       |
| Caelo    | Rue herb, cut      | 12148803      | 2       |
| Caelo    | Rue herb, cut      | 12148804      | 1       |
| Caelo    | Rue herb, cut      | 12148806      | 1       |
| Caelo    | Rue herb, cut      |               | 1       |
| Caelo    | Rue herb, cut      | 12148801      | 1       |
| Caelo    | Saffron filaments  | 10184822      | 1       |
| Caelo    | Saffron filaments  | 11071310      | 1       |
| Caelo    | Saffron filaments  | 21011403      | 1       |
| Caelo    | Saffron filaments  | 15101305      | 1       |
| Caelo    | Saffron filaments  | 12108311      | 2       |
| Caelo    | Saffron filaments  | 10184811      | 2       |
| Caelo    | Saffron filaments  | 12108308      | 2       |
| Caelo    | Sage leaf, cut     | 103311513     | 1       |
| Caelo    | Sage leaf, cut     | 12370013      | 4       |
| Caelo    | Sage leaf, cut     | 12370006      | 7       |
| Caelo    | Sage leaf, cut     | 12370004      | 2       |
| Caelo    | Sage leaf, cut     | 12370003      | 7       |
| Caelo    | Sage leaf, cut     | 12370001      | 19      |
| Caelo    | Sage leaf, cut     | 12112101      | 1       |
| Caelo    | Sage leaf, cut     | 1209211513    | 1       |
| Caelo    | Sage leaf, cut     | 12021302      | 1       |
| Caelo    | Sage leaf, cut     | 11347513      | 3       |
| Caelo    | Sage leaf, cut     | 11347510      | 1       |
| Caelo    | Sage leaf, cut     | 11347508      | 8       |
| Caelo    | Sage leaf, cut     | 12370014      | 9       |
| Caelo    | Sage leaf, cut     | 11347503      | 1       |
| Caelo    | Sage leaf, cut     | 111012004     | 1       |
| Caelo    | Sage leaf, cut     | 11056125      | 3       |
| Caelo    | Sage leaf, cut     | 11056124      | 1       |
| Caelo    | Sage leaf, cut     | 9121302       | 1       |
| Caelo    | Sage leaf, cut     | 8011420       | 1       |
| Caelo    | Sage leaf, cut     | 1104211513    | 1       |

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| <b>Supplier</b> | <b>Substance</b>       | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|------------------------|---------------------|----------------|
| Caelo           | Sage leaf, cut         | 410211513           | 1              |
| Caelo           | Sage leaf, cut         | 11056104            | 1              |
| Caelo           | Sage leaf, cut         | 11056108            | 3              |
| Caelo           | Sage leaf, cut         | 11347509            | 8              |
| Caelo           | Sage leaf, cut         | 12370015            | 2              |
| Caelo           | Sage leaf, cut         | 15041304            | 1              |
| Caelo           | Sage leaf, cut         | 123770010           | 1              |
| Caelo           | Sage leaf, cut         | 19071205            | 1              |
| Caelo           | Sage leaf, cut         | 20121201            | 1              |
| Caelo           | Sage leaf, cut         | 22061201            | 1              |
| Caelo           | Sage leaf, cut         | 22081203            | 1              |
| Caelo           | Sage leaf, cut         | 22111203            | 1              |
| Caelo           | Sage leaf, cut         | 1237003             | 1              |
| Caelo           | Sage leaf, cut         | 11347512            | 1              |
| Caelo           | Sage leaf, cut         | 17061302            | 1              |
| Caelo           | Sage leaf, cut         | 12370003-3359319071 | 1              |
| Caelo           | Sage leaf, cut         | 31081202            | 1              |
| Caelo           | Sage leaf, cut         | 31051315            | 1              |
| Caelo           | Sage leaf, cut         | 2301A110420         | 3              |
| Caelo           | Sage leaf, cut         | 2301A140205         | 1              |
| Caelo           | Sage leaf, cut         | 279939              | 1              |
| Caelo           | Sage leaf, cut         | 2301C130326         | 1              |
| Caelo           | Sage leaf, cut         | 25061302            | 1              |
| Caelo           | Sage leaf, cut         | 312010              | 1              |
| Caelo           | Sage leaf, cut         | 12370017            | 1              |
| Caelo           | Sage leaf, cut         | 1513E-01513         | 1              |
| Caelo           | Sage leaf, cut         | 12370011            | 12             |
| Caelo           | Sage leaf, cut         | 12380009            | 1              |
| Caelo           | Sage leaf, cut         | 13011405            | 1              |
| Caelo           | Sage leaf, cut         | 13266603            | 2              |
| Caelo           | Sage leaf, cut         | 13266605            | 4              |
| Caelo           | Sage leaf, cut         | 13266606            | 1              |
| Caelo           | Sage leaf, cut         | 13266620            | 1              |
| Caelo           | Sage leaf, cut         | 13266621            | 1              |
| Caelo           | Sage leaf, cut         | 12370009            | 12             |
| Caelo           | Sage leaf, cut         | 13266626            | 1              |
| Caelo           | Sage leaf, cut         | 14111315            | 1              |
| Caelo           | Sage leaf, cut         | 23101203            | 1              |
| Caelo           | Sage leaf, cut         | 15090103            | 1              |
| Caelo           | Sage leaf, cut         | 15090112            | 2              |
| Caelo           | Sage leaf, cut         | 12370014-3541411092 | 1              |
| Caelo           | Sage leaf, cut         | 15121201            | 1              |
| Caelo           | Sage leaf, cut         | 12370014-3477312161 | 1              |
| Caelo           | Sage leaf, cut         | 140713b             | 1              |
| Caelo           | Sage leaf, cut         | 24091204            | 1              |
| Caelo           | Sage leaf, cut         | 26081301            | 1              |
| Caelo           | Sarsaparilla root, cut | 13079201            | 1              |
| Caelo           | Savory, rubbed         | 12177203            | 7              |
| Caelo           | Savory, rubbed         | 13172404            | 2              |
| Caelo           | Savory, rubbed         | 12200801            | 1              |
| Caelo           | Savory, rubbed         | 12177208            | 2              |
| Caelo           | Savory, rubbed         | 12177207            | 1              |
| Caelo           | Savory, rubbed         | 12177201            | 1              |
| Caelo           | Senna leaf, cut        | 11277316            | 5              |
| Caelo           | Senna leaf, cut        | 2909211514          | 1              |
| Caelo           | Senna leaf, cut        | 14306324            | 1              |
| Caelo           | Senna leaf, cut        | 12273101            | 6              |
| Caelo           | Senna leaf, cut        | 11277307            | 1              |
| Caelo           | Senna leaf, cut        | 11277304            | 5              |
| Caelo           | Senna leaf, cut        | 12273114            | 2              |

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| Supplier | Substance              | Batch               | Spectra |
|----------|------------------------|---------------------|---------|
| Caelo    | Senna leaf, cut        | 2413Q01514          | 1       |
| Caelo    | Senna leaf, cut        | 2231B13014          | 1       |
| Caelo    | Senna leaf, cut        | 18071201            | 1       |
| Caelo    | Senna leaf, cut        | 313082              | 1       |
| Caelo    | Senna leaf, cut        | 3212E-01514         | 1       |
| Caelo    | Senna leaf, cut        | 3813E1514           | 1       |
| Caelo    | Senna leaf, cut        | 10126502            | 1       |
| Caelo    | Senna leaf, cut        | 11041009            | 1       |
| Caelo    | Senna leaf, cut        | 111113a             | 1       |
| Caelo    | Senna leaf, cut        | 11277301            | 1       |
| Caelo    | Senna leaf, cut        | 11277312            | 1       |
| Caelo    | Senna leaf, cut        | 12115501            | 6       |
| Caelo    | Senna leaf, cut        | 514R1514            | 1       |
| Caelo    | Senna leaf, cut        | 9071302             | 1       |
| Caelo    | Senna leaf, cut        | 5091306             | 1       |
| Caelo    | Senna leaf, cut        | 12115502            | 1       |
| Caelo    | Senna leaf, cut        | 2402221514          | 1       |
| Caelo    | Senna leaf, cut        | 2402211514          | 1       |
| Caelo    | Senna leaf, cut        | 12115503            | 8       |
| Caelo    | Senna leaf, cut        | 12273111            | 11      |
| Caelo    | Senna leaf, cut        | 5013U01514          | 1       |
| Caelo    | Senna leaf, cut        | 4113Q1514           | 1       |
| Caelo    | Senna leaf, cut        | 103311514           | 2       |
| Caelo    | Senna leaf, cut        | 21011401            | 1       |
| Caelo    | Senna leaf, cut        | 806211514           | 1       |
| Caelo    | Senna leaf, cut        | 12273104            | 2       |
| Caelo    | Senna leaf, cut        | 14306311            | 2       |
| Caelo    | Senna leaf, cut        | 14306310            | 1       |
| Caelo    | Senna leaf, cut        | 14183805            | 3       |
| Caelo    | Senna leaf, cut        | 1316706             | 1       |
| Caelo    | Senna leaf, cut        | 1316703             | 2       |
| Caelo    | Senna leaf, cut        | 13136724            | 2       |
| Caelo    | Senna leaf, cut        | 13136718            | 1       |
| Caelo    | Senna leaf, cut        | 13136709            | 1       |
| Caelo    | Senna leaf, cut        | 13136706            | 1       |
| Caelo    | Senna leaf, cut        | 13136705            | 2       |
| Caelo    | Senna leaf, cut        | 13136703            | 3       |
| Caelo    | Senna leaf, cut        | 12273115            | 11      |
| Caelo    | Senna leaf, cut        | 131316701           | 1       |
| Caelo    | Senna leaf, cut        | 1273103             | 1       |
| Caelo    | Senna leaf, cut        | 12369903            | 1       |
| Caelo    | Senna leaf, cut        | 711211514           | 1       |
| Caelo    | Senna leaf, cut        | 13136705-3489312103 | 1       |
| Caelo    | Senna leaf, cut        | 12273120            | 3       |
| Caelo    | Senna leaf, cut        | 12273116            | 19      |
| Caelo    | Senna leaf, cut        | 12273105            | 7       |
| Caelo    | Senna leaf, cut        | 15101303            | 1       |
| Caelo    | Senna leaf, cut        | 13136704            | 15      |
| Caelo    | Senna leaf, cut        | 12273118            | 6       |
| Caelo    | Senna leaf, cut        | 12273106            | 3       |
| Caelo    | Senna leaf, cut        | 12273113            | 3       |
| Caelo    | Senna leaf, cut        | 12273107            | 10      |
| Caelo    | Senna leaf, cut        | 12273119            | 4       |
| Caelo    | Senna leaf, cut        | 1803311514          | 1       |
| Caelo    | Senna leaf, cut        | 12276111            | 1       |
| Caelo    | Senna leaf, powdered   | 14088703            | 1       |
| Caelo    | Senna leaf, powdered   | 11193307            | 1       |
| Caelo    | Senna pods, tinnevelly | 12267605            | 1       |
| Caelo    | Senna pods, tinnevelly | 110030009           | 1       |
| Caelo    | Senna pods, tinnevelly | 12267604            | 1       |

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| <b>Supplier</b> | <b>Substance</b>       | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|------------------------|---------------------|----------------|
| Caelo           | Senna pods, tinnevelly | 12267608            | 1              |
| Caelo           | Senna pods, tinnevelly | 11003013            | 1              |
| Caelo           | Senna pods, tinnevelly | 12267201            | 1              |
| Caelo           | Senna pods, tinnevelly | 11003004            | 1              |
| Caelo           | Senna pods, tinnevelly | 22061202            | 1              |
| Caelo           | Senna pods, tinnevelly | 12267610            | 1              |
| Caelo           | Senna pods, tinnevelly | 12267609            | 4              |
| Caelo           | Senna pods, tinnevelly | 122676707           | 1              |
| Caelo           | Senna pods, tinnevelly | 11003009            | 2              |
| Caelo           | Senna pods, tinnevelly | 12267602            | 1              |
| Caelo           | Senna pods, tinnevelly | 12267606            | 1              |
| Caelo           | Shepherd's purse, cut  | 11328208            | 6              |
| Caelo           | Shepherd's purse, cut  | 12354201            | 15             |
| Caelo           | Shepherd's purse, cut  | 12354206            | 4              |
| Caelo           | Shepherd's purse, cut  | 12354209            | 1              |
| Caelo           | Shepherd's purse, cut  | 12354503            | 1              |
| Caelo           | Shepherd's purse, cut  | 13344203            | 1              |
| Caelo           | Shepherd's purse, cut  | 14061201            | 1              |
| Caelo           | Shepherd's purse, cut  | 15101202            | 1              |
| Caelo           | Shepherd's purse, cut  | 11036406            | 8              |
| Caelo           | Shepherd's purse, cut  | 12354207            | 2              |
| Caelo           | Shepherd's purse, cut  | 12354203-3396310111 | 1              |
| Caelo           | Shepherd's purse, cut  | 11328201            | 8              |
| Caelo           | Shepherd's purse, cut  | 4411E-01625         | 1              |
| Caelo           | Shepherd's purse, cut  | 11036401            | 1              |
| Caelo           | Shepherd's purse, cut  | 11328207            | 10             |
| Caelo           | Shepherd's purse, cut  | 12354205            | 6              |
| Caelo           | Shepherd's purse, cut  | 12354204            | 20             |
| Caelo           | Shepherd's purse, cut  | 12354203            | 11             |
| Caelo           | Shepherd's purse, cut  | 11036404            | 2              |
| Caelo           | Shepherd's purse, cut  | 12254202            | 1              |
| Caelo           | Shepherd's purse, cut  | 11328209            | 6              |
| Caelo           | Shepherd's purse, cut  | 11328206            | 2              |
| Caelo           | Shepherd's purse, cut  | 11328203            | 7              |
| Caelo           | Shepherd's purse, cut  | 11328205            | 2              |
| Caelo           | Shepherd's purse, cut  | 11328204            | 4              |
| Caelo           | Shepherd's purse, cut  | 10061301            | 1              |
| Caelo           | Shepherd's purse, cut  | 12354202            | 2              |
| Caelo           | Shepherd's purse, cut  | 3121301             | 1              |
| Caelo           | Shepherd's purse, cut  | 11328202            | 1              |
| Caelo           | Shepherd's purse, cut  | 1132820111-14       | 1              |
| Caelo           | Shepherd's purse, cut  | 11091202            | 1              |
| Caelo           | Silverweed, cut        | 11328109            | 15             |
| Caelo           | Silverweed, cut        | 11016401            | 1              |
| Caelo           | Silverweed, cut        | 11328110            | 1              |
| Caelo           | Silverweed, cut        | 5012E-01619         | 1              |
| Caelo           | Silverweed, cut        | 13410801            | 1              |
| Caelo           | Silverweed, cut        | 11016407            | 2              |
| Caelo           | Silverweed, cut        | 11016409            | 3              |
| Caelo           | Silverweed, cut        | 11328112            | 2              |
| Caelo           | Silverweed, cut        | 11328104            | 1              |
| Caelo           | Silverweed, cut        | 11328105            | 7              |
| Caelo           | Silverweed, cut        | 11326102            | 1              |
| Caelo           | Silverweed, cut        | 20081202            | 1              |
| Caelo           | Silverweed, cut        | 11328103            | 5              |
| Caelo           | Silverweed, cut        | 9362614             | 1              |
| Caelo           | Silverweed, cut        | 8111204             | 1              |
| Caelo           | Silverweed, cut        | 11016404            | 1              |
| Caelo           | Silverweed, cut        | 9362606             | 1              |
| Caelo           | Silverweed, cut        | 11016404            | 1              |

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| Supplier | Substance                | Batch       | Spectra |
|----------|--------------------------|-------------|---------|
| Caelo    | Silverweed, cut          | 11016405    | 1       |
| Caelo    | Sodium carbonate deca... | 11254708    | 2       |
| Caelo    | Sodium carbonate deca... | 12239810    | 3       |
| Caelo    | Sodium carbonate deca... | 12239806    | 1       |
| Caelo    | Sodium carbonate deca... | 80136179    | 1       |
| Caelo    | Sodium carbonate deca... | 80136428    | 1       |
| Caelo    | Sodium carbonate deca... | 13036909    | 1       |
| Caelo    | Sodium carbonate deca... | 13036902    | 3       |
| Caelo    | Sodium carbonate deca... | 13036907    | 1       |
| Caelo    | Sodium carbonate deca... | 13036910    | 1       |
| Caelo    | Sodium carbonate deca... | 11254706    | 1       |
| Caelo    | Sodium dihydrogen pho... | 12198506    | 1       |
| Caelo    | Sodium dihydrogen pho... | 12198510    | 2       |
| Caelo    | Sodium dihydrogen pho... | 12198517    | 3       |
| Caelo    | Sodium dihydrogen pho... | 11277504    | 1       |
| Caelo    | Sodium dihydrogen pho... | 13D08-N25   | 1       |
| Caelo    | Sodium dihydrogen pho... | 15122808    | 1       |
| Caelo    | Sodium hydrogen carbo... | 6011404     | 1       |
| Caelo    | Sodium hydrogen carbo... | 12324702    | 9       |
| Caelo    | Sodium hydrogen carbo... | 12324708    | 1       |
| Caelo    | Sodium hydrogen carbo... | 12324725    | 2       |
| Caelo    | Sodium hydrogen carbo... | 1307017-02  | 1       |
| Caelo    | Sodium hydrogen carbo... | 130701701   | 1       |
| Caelo    | Sodium hydrogen carbo... | 13186711    | 1       |
| Caelo    | Sodium hydrogen carbo... | 1307017-01  | 2       |
| Caelo    | Sodium hydrogen carbo... | 13186705    | 3       |
| Caelo    | Sodium hydrogen carbo... | 13060103    | 12      |
| Caelo    | Sodium hydrogen carbo... | 12109204    | 6       |
| Caelo    | Sodium hydrogen carbo... | 12109202    | 1       |
| Caelo    | Sodium hydrogen carbo... | 13060104    | 1       |
| Caelo    | Sodium hydrogen carbo... | 13060117    | 1       |
| Caelo    | Sodium hydrogen carbo... | 12356407    | 2       |
| Caelo    | Sodium hydrogen carbo... | 12324703    | 1       |
| Caelo    | Sodium hydrogen carbo... | 12132213    | 1       |
| Caelo    | Sodium hydrogen carbo... | 12356403    | 1       |
| Caelo    | Sodium hydrogen carbo... | 12356401    | 4       |
| Caelo    | Sodium hydrogen carbo... | 11304809    | 2       |
| Caelo    | Sodium hydrogen carbo... | 1219204     | 1       |
| Caelo    | Sodium hydrogen carbo... | 12132503    | 1       |
| Caelo    | Sodium hydrogen carbo... | 12132219    | 10      |
| Caelo    | Sodium hydrogen carbo... | 12132204    | 11      |
| Caelo    | Sodium hydrogen carbo... | 11304802    | 3       |
| Caelo    | Sodium hydrogen carbo... | 13390505    | 1       |
| Caelo    | Sodium hydrogen carbo... | 13390520    | 1       |
| Caelo    | Sodium hydrogen carbo... | 15328602    | 1       |
| Caelo    | Sodium hydrogen carbo... | 21081204    | 1       |
| Caelo    | Sodium hydrogen carbo... | 3012Q-01892 | 1       |
| Caelo    | Sodium hydrogen carbo... | 3313I-01892 | 1       |
| Caelo    | Sodium hydrogen carbo... | 11304813    | 2       |
| Caelo    | Sodium hydrogen carbo... | 13234205    | 1       |
| Caelo    | Sodium hydrogen carbo... | 8101203     | 1       |
| Caelo    | Sodium hydrogen carbo... | 13234202    | 3       |
| Caelo    | Sodium hydrogen carbo... | 1203030-1   | 1       |
| Caelo    | Sodium hydrogen carbo... | 12109205    | 7       |
| Caelo    | Sodium hydrogen carbo... | 13234005    | 4       |
| Caelo    | Sodium hydrogen carbo... | 13234004    | 2       |
| Caelo    | Sodium hydrogen carbo... | 13186721    | 1       |
| Caelo    | Sodium hydrogen carbo... | 1234702     | 2       |
| Caelo    | Sodium hydrogen carbo... | 13186706    | 1       |
| Caelo    | Sodium hydrogen carbo... | 12132203    | 4       |

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| Supplier | Substance                | Batch       | Spectra |
|----------|--------------------------|-------------|---------|
| Caelo    | Sodium hydrogen carbo... | 13186704    | 1       |
| Caelo    | Sodium hydrogen carbo... | 13234007    | 4       |
| Caelo    | Sodium hydrogen carbo... | 12356303    | 3       |
| Caelo    | Sodium hydrogen carbo... | 13060120    | 7       |
| Caelo    | Sodium hydroxide pell... | 15312102    | 1       |
| Caelo    | Sodium hydroxide pell... | 11070821    | 1       |
| Caelo    | Sodium hydroxide pell... | 12368105    | 2       |
| Caelo    | Sodium monohydrogenph... | 9302617     | 1       |
| Caelo    | Sodium monohydrogenph... | 83002059    | 1       |
| Caelo    | Sodium monohydrogenph... | AKD7        | 1       |
| Caelo    | Sodium monohydrogenph... | 12345025    | 1       |
| Caelo    | Sodium monohydrogenph... | 12345016    | 9       |
| Caelo    | Sodium monohydrogenph... | 12345004    | 8       |
| Caelo    | Sodium monohydrogenph... | 12256606    | 5       |
| Caelo    | Sodium monohydrogenph... | 12256602    | 4       |
| Caelo    | Sodium monohydrogenph... | 71199028    | 1       |
| Caelo    | Sodium monohydrogenph... | 12345001    | 7       |
| Caelo    | Sodium monohydrogenph... | 1169315     | 1       |
| Caelo    | Sodium monohydrogenph... | 11169321    | 1       |
| Caelo    | Sodium monohydrogenph... | 11169309    | 3       |
| Caelo    | Sodium monohydrogenph... | 11169303    | 2       |
| Caelo    | Sodium monohydrogenph... | 11169301    | 1       |
| Caelo    | Sodium monohydrogenph... | 8300209     | 1       |
| Caelo    | Sodium monohydrogenph... | 11169315    | 4       |
| Caelo    | Sodium monohydrogenph... | 9302613     | 2       |
| Caelo    | Sodium monohydrogenph... | 12345007    | 6       |
| Caelo    | Sodium monohydrogenph... | 28131-01914 | 1       |
| Caelo    | Sodium monohydrogenph... | 13028003    | 1       |
| Caelo    | Sodium monohydrogenph... | 13028001    | 4       |
| Caelo    | Sodium monohydrogenph... | 12109109    | 1       |
| Caelo    | Sodium monohydrogenph... | 72006059    | 1       |
| Caelo    | Sodium monohydrogenph... | 12109003    | 3       |
| Caelo    | Sodium monohydrogenph... | 12109108    | 2       |
| Caelo    | Sodium monohydrogenph... | 12109106    | 2       |
| Caelo    | Sodium monohydrogenph... | 12109102    | 1       |
| Caelo    | Sodium monohydrogenph... | 12109101    | 2       |
| Caelo    | Sodium monohydrogenph... | 12109002    | 4       |
| Caelo    | Sodium monohydrogenph... | 11109513    | 1       |
| Caelo    | Sodium monohydrogenph... | 10135304    | 1       |
| Caelo    | Sodium monohydrogenph... | 13028103    | 1       |
| Caelo    | Sodium monohydrogenph... | 12109104    | 1       |
| Caelo    | Sodium perborate, hyd... | 13050807    | 1       |
| Caelo    | Sodium perborate, hyd... | 13050801    | 2       |
| Caelo    | Sodium perborate, hyd... | 13050805    | 2       |
| Caelo    | Sodium sulfate decahy... | 12157017    | 1       |
| Caelo    | Sodium sulfate decahy... | 70706387    | 1       |
| Caelo    | Sodium sulfate decahy... | 12157005    | 20      |
| Caelo    | Sodium sulfate decahy... | 12157011    | 1       |
| Caelo    | Sodium sulfate decahy... | 61599506    | 1       |
| Caelo    | Sodium sulfate decahy... | 18101202    | 1       |
| Caelo    | Sodium sulfate decahy... | 12257901    | 11      |
| Caelo    | Sodium sulfate decahy... | 12257902    | 8       |
| Caelo    | Sodium sulfate decahy... | 12256902    | 1       |
| Caelo    | Sodium sulfate decahy... | 12157013    | 4       |
| Caelo    | Sodium sulfate decahy... | 12157006    | 11      |
| Caelo    | Sodium sulfate decahy... | 12157007    | 1       |
| Caelo    | Sodium sulfate decahy... | 11294501    | 1       |
| Caelo    | Sodium sulfate decahy... | 12157001    | 4       |
| Caelo    | Sodium sulfate decahy... | 2013A-01920 | 1       |
| Caelo    | Sodium sulfate decahy... | 11012207    | 1       |

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| Supplier | Substance                | Batch           | Spectra |
|----------|--------------------------|-----------------|---------|
| Caelo    | Sodium sulfate decahy... | 12157012        | 22      |
| Caelo    | Sodium sulfate decahy... | 205026          | 1       |
| Caelo    | Sodium sulfate decahy... | 11294605        | 2       |
| Caelo    | Sodium sulfate decahy... | 11294504        | 1       |
| Caelo    | Sodium sulfate decahy... | 11012210        | 2       |
| Caelo    | Sodium thiosulfate pe... | 80426288        | 1       |
| Caelo    | Sodium thiosulfate pe... | 26041302        | 1       |
| Caelo    | Solanum dulcamara ste... | 10375605        | 1       |
| Caelo    | Solanum dulcamara ste... | 132564301       | 1       |
| Caelo    | Solanum dulcamara ste... | 4712M-02335     | 1       |
| Caelo    | Solanum dulcamara ste... | 10375603        | 2       |
| Caelo    | Solanum dulcamara ste... | 10375604        | 2       |
| Caelo    | Solanum dulcamara ste... | 103745604       | 1       |
| Caelo    | Solanum dulcamara ste... | 13254301        | 1       |
| Caelo    | Sorrel herb, cut         | 11165310        | 1       |
| Caelo    | Sorrel herb, cut         | 13289502        | 2       |
| Caelo    | Sorrel herb, cut         | 11165302        | 1       |
| Caelo    | Sorrel herb, cut         | 130546          | 1       |
| Caelo    | Sour cherry stems, cut   | 10367019        | 1       |
| Caelo    | Sour cherry stems, cut   | 10367014        | 1       |
| Caelo    | Sour cherry stems, cut   | 12042301        | 1       |
| Caelo    | Sour cherry stems, cut   | 12042307        | 1       |
| Caelo    | Spearmint leaf, cut      | 1512Q-01505     | 1       |
| Caelo    | Spearmint leaf, cut      | 12376706        | 2       |
| Caelo    | Spearmint leaf, cut      | 12133909        | 1       |
| Caelo    | Spearmint leaf, cut      | 12133906        | 2       |
| Caelo    | Spearmint leaf, cut      | 12133901        | 3       |
| Caelo    | Spearmint leaf, cut      | 11037409+110374 | 1       |
| Caelo    | Spearmint leaf, cut      | 13105003        | 1       |
| Caelo    | Spearmint leaf, cut      | 13105001        | 12      |
| Caelo    | St. John's wort, cut     | 13203205        | 1       |
| Caelo    | St. John's wort, cut     | 132203204       | 1       |
| Caelo    | St. John's wort, cut     | 13091303        | 1       |
| Caelo    | St. John's wort, cut     | 13203204        | 7       |
| Caelo    | St. John's wort, cut     | 15068105        | 1       |
| Caelo    | St. John's wort, cut     | 30011401        | 1       |
| Caelo    | St. John's wort, cut     | 268913          | 1       |
| Caelo    | St. John's wort, cut     | 12092202        | 8       |
| Caelo    | St. John's wort, cut     | 3213A-01655     | 1       |
| Caelo    | St. John's wort, cut     | 4021A100819     | 3       |
| Caelo    | St. John's wort, cut     | 4021B110321     | 1       |
| Caelo    | St. John's wort, cut     | 16041301        | 1       |
| Caelo    | St. John's wort, cut     | 12092204        | 1       |
| Caelo    | St. John's wort, cut     | 12092209        | 2       |
| Caelo    | St. John's wort, cut     | 12092201        | 2       |
| Caelo    | St. John's wort, cut     | 1185608         | 1       |
| Caelo    | St. John's wort, cut     | 11185608        | 22      |
| Caelo    | St. John's wort, cut     | 11185603        | 1       |
| Caelo    | St. John's wort, cut     | 11185607        | 2       |
| Caelo    | St. John's wort, cut     | 11185605        | 6       |
| Caelo    | St. John's wort, cut     | 11185602        | 2       |
| Caelo    | St. John's wort, cut     | 5021301         | 1       |
| Caelo    | St. John's wort, cut     | 5061208         | 1       |
| Caelo    | St. John's wort, cut     | 111185608       | 1       |
| Caelo    | St. John's wort, cut     | 12092203        | 1       |
| Caelo    | St. John's wort, cut     | 9297304         | 1       |
| Caelo    | Star anise               | 10376405        | 1       |
| Caelo    | Star anise               | 10169101        | 1       |
| Caelo    | Star anise               | 11314103        | 3       |
| Caelo    | Star anise               | 11314104        | 1       |

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| Supplier | Substance                | Batch       | Spectra |
|----------|--------------------------|-------------|---------|
| Caelo    | Star anise               | 5111206     | 1       |
| Caelo    | Star anise               | 12226211    | 1       |
| Caelo    | Stemless carline root    | 12163701    | 3       |
| Caelo    | Stemless carline root    | 13033501    | 1       |
| Caelo    | Stemless carline root    | 12144804    | 1       |
| Caelo    | Stemless carline root    | 23071203    | 1       |
| Caelo    | Stemless carline root    | 13130303    | 1       |
| Caelo    | Stemless carline root    | 13130301    | 7       |
| Caelo    | Stemless carline root    | 13130304    | 1       |
| Caelo    | Stemless carline root    | 13130903    | 1       |
| Caelo    | Stemless carline root    | 14347401    | 1       |
| Caelo    | Stemless carline root    | 25111306    | 1       |
| Caelo    | Stemless carline root    | 12232803    | 1       |
| Caelo    | Strawberry leaf, cut     | 4512A-01490 | 1       |
| Caelo    | Strawberry leaf, cut     | 11117909    | 1       |
| Caelo    | Strawberry leaf, cut     | 5122013c    | 1       |
| Caelo    | Sulfamerazine            | 10218401    | 1       |
| Caelo    | Sunflower, cut           | 313A-03521  | 1       |
| Caelo    | Sweet woodruff herb, ... | 52236077    | 1       |
| Caelo    | Sweet woodruff herb, ... | 4409M-01621 | 1       |
| Caelo    | Sweet woodruff herb, ... | 18031304    | 1       |
| Caelo    | Sweet woodruff herb, ... | 12103514    | 1       |
| Caelo    | Sweet woodruff herb, ... | 12103513    | 2       |
| Caelo    | Sweet woodruff herb, ... | 12103510    | 1       |
| Caelo    | Sweet woodruff herb, ... | 12103509    | 3       |
| Caelo    | Sweet woodruff herb, ... | 91789309    | 1       |
| Caelo    | Sweet woodruff herb, ... | 10375802    | 1       |
| Caelo    | Sweet woodruff herb, ... | 10375812    | 2       |
| Caelo    | Sweet woodruff herb, ... | nachprüfung | 2       |
| Caelo    | Sweet woodruff herb, ... | 10375809    | 2       |
| Caelo    | Talcum                   | 12111301    | 1       |
| Caelo    | Talcum                   | 12267401    | 5       |
| Caelo    | Talcum                   | 11318324    | 4       |
| Caelo    | Talcum                   | 11318311    | 3       |
| Caelo    | Talcum                   | 11318312    | 2       |
| Caelo    | Talcum                   | 11318323    | 1       |
| Caelo    | Talcum                   | 13146316    | 3       |
| Caelo    | Talcum                   | 13146307    | 4       |
| Caelo    | Talcum                   | 11318335    | 4       |
| Caelo    | Talcum                   | 15061301    | 1       |
| Caelo    | Talcum                   | 1205046-01  | 3       |
| Caelo    | Talcum                   | 28121201    | 1       |
| Caelo    | Talcum                   | 11318301    | 1       |
| Caelo    | Talcum                   | 12267424    | 6       |
| Caelo    | Talcum                   | 11164306    | 2       |
| Caelo    | Talcum                   | 12267412    | 8       |
| Caelo    | Talcum                   | 9218303     | 1       |
| Caelo    | Talcum                   | 2011406     | 1       |
| Caelo    | Talcum                   | 13146312    | 5       |
| Caelo    | Talcum                   | 13146308    | 7       |
| Caelo    | Talcum                   | 12267423    | 3       |
| Caelo    | Talcum                   | 13146302    | 11      |
| Caelo    | Talcum                   | 13146315    | 1       |
| Caelo    | Talcum                   | 11164313    | 1       |
| Caelo    | Tall golden rod, cut     | 112080308   | 1       |
| Caelo    | Tall golden rod, cut     | 15061203    | 1       |
| Caelo    | Tall golden rod, cut     | 4091302     | 1       |
| Caelo    | Tall golden rod, cut     | 4021405     | 1       |
| Caelo    | Tall golden rod, cut     | 2656153     | 1       |
| Caelo    | Tall golden rod, cut     | 11280308    | 14      |

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| Supplier | Substance                | Batch       | Spectra |
|----------|--------------------------|-------------|---------|
| Caelo    | Tall golden rod, cut     | 11280305    | 3       |
| Caelo    | Tall golden rod, cut     | 11280301    | 8       |
| Caelo    | Tall golden rod, cut     | 11207010    | 3       |
| Caelo    | Tall golden rod, cut     | 11085605    | 2       |
| Caelo    | Tall golden rod, cut     | 6081302     | 1       |
| Caelo    | Tall golden rod, cut     | 11280307    | 1       |
| Caelo    | Tall golden rod, cut     | 12319003    | 24      |
| Caelo    | Tall golden rod, cut     | 11280310    | 6       |
| Caelo    | Tall golden rod, cut     | 1810201204  | 1       |
| Caelo    | Tall golden rod, cut     | 14018404    | 1       |
| Caelo    | Tall golden rod, cut     | 13386903    | 1       |
| Caelo    | Tall golden rod, cut     | 13386901    | 2       |
| Caelo    | Tall golden rod, cut     | 13049001    | 1       |
| Caelo    | Tall golden rod, cut     | 12343109    | 1       |
| Caelo    | Tall golden rod, cut     | 12343105    | 1       |
| Caelo    | Tall golden rod, cut     | 12343104    | 9       |
| Caelo    | Tall golden rod, cut     | 12343103    | 18      |
| Caelo    | Tall golden rod, cut     | 12343102    | 5       |
| Caelo    | Tall golden rod, cut     | 12343101    | 2       |
| Caelo    | Tall golden rod, cut     | 12336801    | 1       |
| Caelo    | Tall golden rod, cut     | 12319007    | 31      |
| Caelo    | Tall golden rod, cut     | 12319006    | 6       |
| Caelo    | Tall golden rod, cut     | 12319004    | 13      |
| Caelo    | Tall golden rod, cut     | nachprüfung | 1       |
| Caelo    | Tall golden rod, cut     | 12319002    | 2       |
| Caelo    | Tall golden rod, cut     | 11280309    | 3       |
| Caelo    | Tall golden rod, cut     | 20111209    | 1       |
| Caelo    | Tall golden rod, cut     | 17091203    | 1       |
| Caelo    | Tall golden rod, cut     | 14112012    | 1       |
| Caelo    | Tall golden rod, cut     | 2513A-01684 | 1       |
| Caelo    | Tall golden rod, cut     | 12343106    | 1       |
| Caelo    | Tall golden rod, cut     | 12343108    | 1       |
| Caelo    | Tall golden rod, cut     | 27121302    | 1       |
| Caelo    | Tall golden rod, cut     | 28051302    | 1       |
| Caelo    | Tall golden rod, cut     | 314050-1-p  | 1       |
| Caelo    | Tall golden rod, cut     | 4113A-01684 | 1       |
| Caelo    | Tall hawkweed, cut       | 3611B111005 | 2       |
| Caelo    | Tall hawkweed, cut       | 3611b111005 | 1       |
| Caelo    | Tall nasturtium herb,... | 107063      | 1       |
| Caelo    | Tall nasturtium herb,... | 12031604    | 2       |
| Caelo    | Tall nasturtium herb,... | 13104406    | 1       |
| Caelo    | Tall nasturtium herb,... | 12031601    | 1       |
| Caelo    | Tall nasturtium herb,... | 13104401    | 4       |
| Caelo    | Tall nasturtium herb,... | 13104402    | 2       |
| Caelo    | Tall nasturtium herb,... | 12031605    | 1       |
| Caelo    | Tall nasturtium herb,... | 12031603    | 1       |
| Caelo    | Tall nasturtium herb,... | 13104404    | 2       |
| Caelo    | Tall nasturtium herb,... | 12031602    | 1       |
| Caelo    | Tall nasturtium herb,... | 13104405    | 1       |
| Caelo    | Tall nasturtium herb,... | 12031606    | 1       |
| Caelo    | Tall nasturtium herb,... | 10224507    | 1       |
| Caelo    | Tall nasturtium herb,... | 13104403    | 4       |
| Caelo    | Theriac, powdered        | 12289306    | 1       |
| Caelo    | Theriac, powdered        | 4714M-07000 | 1       |
| Caelo    | Theriac, powdered        | 412091-2P   | 1       |
| Caelo    | Theriac, powdered        | 12289303    | 1       |
| Caelo    | Theriac, powdered        | 15312504    | 2       |
| Caelo    | Theriac, powdered        | 12189404    | 2       |
| Caelo    | Theriac, powdered        | 11082413    | 1       |
| Caelo    | Theriac, powdered        | 12289312    | 1       |

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| <b>Supplier</b> | <b>Substance</b>  | <b>Batch</b> | <b>Spectra</b> |
|-----------------|-------------------|--------------|----------------|
| Caelo           | Theriac, powdered | 13407303     | 1              |
| Caelo           | Theriac, powdered | 12289305     | 3              |
| Caelo           | Theriac, powdered | 12289301     | 4              |
| Caelo           | Theriac, powdered | 15312501     | 1              |
| Caelo           | Theriac, powdered | 14156501     | 1              |
| Caelo           | Theriac, powdered | 13407304     | 2              |
| Caelo           | Theriac, powdered | 12289307     | 9              |
| Caelo           | Theriac, powdered | 11081515     | 1              |
| Caelo           | Theriac, powdered | 12289304     | 1              |
| Caelo           | Theriac, powdered | 12189401     | 4              |
| Caelo           | Theriac, powdered | 1513E-01351  | 1              |
| Caelo           | Theriac, powdered | 15101307     | 1              |
| Caelo           | Theriac, powdered | 15026403     | 1              |
| Caelo           | Theriac, powdered | 2021301      | 1              |
| Caelo           | Theriac, powdered | 11082408     | 1              |
| Caelo           | Theriac, powdered | 13407306     | 1              |
| Caelo           | Theriac, powdered | 11082409     | 1              |
| Caelo           | Thiomersal        | 21051507     | 1              |
| Caelo           | Thiomersal        | 10296413     | 1              |
| Caelo           | Thyme, rubbed     | 11021301     | 1              |
| Caelo           | Thyme, rubbed     | 13048309     | 6              |
| Caelo           | Thyme, rubbed     | 13048308     | 2              |
| Caelo           | Thyme, rubbed     | 25091208     | 1              |
| Caelo           | Thyme, rubbed     | 4041301      | 1              |
| Caelo           | Thyme, rubbed     | 29101301     | 1              |
| Caelo           | Thyme, rubbed     | 11121306     | 1              |
| Caelo           | Thyme, rubbed     | 1134006      | 1              |
| Caelo           | Thyme, rubbed     | 21121204     | 1              |
| Caelo           | Thyme, rubbed     | 23021304     | 1              |
| Caelo           | Thyme, rubbed     | 25041302     | 1              |
| Caelo           | Thyme, rubbed     | 11345003     | 2              |
| Caelo           | Thyme, rubbed     | 11345010     | 7              |
| Caelo           | Thyme, rubbed     | 22021301     | 1              |
| Caelo           | Thyme, rubbed     | 13048301     | 18             |
| Caelo           | Thyme, rubbed     | 26021301     | 1              |
| Caelo           | Thyme, rubbed     | 13011402     | 1              |
| Caelo           | Thyme, rubbed     | 130448301    | 1              |
| Caelo           | Thyme, rubbed     | 6111205      | 1              |
| Caelo           | Thyme, rubbed     | 11345001     | 2              |
| Caelo           | Thyme, rubbed     | 12111201     | 1              |
| Caelo           | Thyme, rubbed     | 13081301     | 1              |
| Caelo           | Thyme, rubbed     | 4021512      | 1              |
| Caelo           | Thyme, rubbed     | 14119001     | 2              |
| Caelo           | Thyme, rubbed     | 15101201     | 1              |
| Caelo           | Thyme, rubbed     | 1134514      | 1              |
| Caelo           | Thyme, rubbed     | 9366310      | 1              |
| Caelo           | Thyme, rubbed     | 11345013     | 7              |
| Caelo           | Thyme, rubbed     | 25091304     | 1              |
| Caelo           | Thyme, rubbed     | 13048302     | 2              |
| Caelo           | Thyme, rubbed     | 13048313     | 2              |
| Caelo           | Thyme, rubbed     | 10365807     | 4              |
| Caelo           | Thyme, rubbed     | 10365803     | 1              |
| Caelo           | Thyme, rubbed     | 10365816     | 3              |
| Caelo           | Thyme, rubbed     | 4622A120111  | 57             |
| Caelo           | Thyme, rubbed     | 273909       | 4              |
| Caelo           | Thyme, rubbed     | 15104401     | 1              |
| Caelo           | Thyme, rubbed     | 11345011     | 19             |
| Caelo           | Thyme, rubbed     | 11345004     | 6              |
| Caelo           | Thyme, rubbed     | 13048314     | 1              |
| Caelo           | Thyme, rubbed     | 11345006     | 9              |

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| Supplier | Substance            | Batch               | Spectra |
|----------|----------------------|---------------------|---------|
| Caelo    | Thyme, rubbed        | 1021307             | 1       |
| Caelo    | Thyme, rubbed        | 10365815            | 5       |
| Caelo    | Thyme, rubbed        | 1213Q-01688         | 1       |
| Caelo    | Thyme, rubbed        | 15104301            | 1       |
| Caelo    | Thyme, rubbed        | 13048309-3475312161 | 1       |
| Caelo    | Thyme, rubbed        | 16011401            | 1       |
| Caelo    | Thyme, rubbed        | 8061206             | 1       |
| Caelo    | Thyme, rubbed        |                     | 2       |
| Caelo    | Thyme, rubbed        | 29011303            | 1       |
| Caelo    | Thyme, rubbed        | 4622A110728         | 40      |
| Caelo    | Tonka beans          | 1078C               | 1       |
| Caelo    | Tonka beans          | 12144101            | 1       |
| Caelo    | Tonka beans          | 12145101            | 3       |
| Caelo    | Tonka beans          | 20111312            | 1       |
| Caelo    | Tormentil            | 12216802            | 1       |
| Caelo    | Tormentil            | 12216803            | 4       |
| Caelo    | Tormentil            | 10081203            | 1       |
| Caelo    | Tormentil            | 15364302            | 3       |
| Caelo    | Tormentil            | 12040717            | 1       |
| Caelo    | Tormentil            | 12040702            | 1       |
| Caelo    | Tormentil            | 12040715            | 1       |
| Caelo    | Tormentil            | 12040709            | 1       |
| Caelo    | Tormentil            | 11102011            | 1       |
| Caelo    | Tormentil            | 12040704            | 2       |
| Caelo    | Tormentil            | 11102010            | 2       |
| Caelo    | Tormentil            | 15178202            | 2       |
| Caelo    | Tormentil            | 12216805            | 1       |
| Caelo    | Tormentil            | 15085501            | 1       |
| Caelo    | Tormentil            | 15178206            | 1       |
| Caelo    | Tormentil            | 14140001            | 1       |
| Caelo    | Tormentil            | 521305-420          | 1       |
| Caelo    | Tormentil            | 14140006            | 4       |
| Caelo    | Tormentil            | 14008001            | 3       |
| Caelo    | Tormentil            | 12216806            | 1       |
| Caelo    | Tormentil            | 12216801            | 5       |
| Caelo    | Tormentil            | 15178203            | 1       |
| Caelo    | Tormentil            | 14360103            | 1       |
| Caelo    | Tormentil            | 14008005            | 1       |
| Caelo    | Tormentil            | 14008002            | 2       |
| Caelo    | Tormentil            | 1914A-02188         | 1       |
| Caelo    | Tormentil            | 13220502            | 1       |
| Caelo    | Tormentil            | 12040701            | 1       |
| Caelo    | Tormentil            | 4753268             | 1       |
| Caelo    | Tormentil            | 25022014A           | 1       |
| Caelo    | Tormentil            | 2512A-02188         | 1       |
| Caelo    | Tormentil            | 411082-2-P          | 1       |
| Caelo    | Tormentil            | 30011405            | 1       |
| Caelo    | Tragacanth, powdered | 13277802            | 4       |
| Caelo    | Tragacanth, powdered | 13204701            | 6       |
| Caelo    | Tragacanth, powdered | 13277801            | 1       |
| Caelo    | Tragacanth, powdered | 14011302            | 1       |
| Caelo    | Tragacanth, powdered | 14162207            | 1       |
| Caelo    | Tragacanth, powdered | 15085602            | 1       |
| Caelo    | Tragacanth, powdered | 14162204            | 1       |
| Caelo    | Tragacanth, powdered | 1327802             | 1       |
| Caelo    | Tragacanth, powdered | 20111305            | 1       |
| Caelo    | Tragacanth, powdered | 13204702            | 1       |
| Caelo    | Tragacanth, powdered | 13204703            | 3       |
| Caelo    | Tragacanth, powdered | 12285408            | 1       |
| Caelo    | Tragacanth, powdered | 12285405            | 1       |

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| <b>Supplier</b> | <b>Substance</b>        | <b>Batch</b> | <b>Spectra</b> |
|-----------------|-------------------------|--------------|----------------|
| Caelo           | Tragacanth, powdered    | 1228503      | 1              |
| Caelo           | Tragacanth, powdered    | 12108806     | 2              |
| Caelo           | Tragacanth, powdered    | 13204705     | 7              |
| Caelo           | Tragacanth, powdered    | 16110802     | 1              |
| Caelo           | Tragacanth, powdered    | 13277804     | 3              |
| Caelo           | Tragacanth, powdered    | 14162207     | 1              |
| Caelo           | Tragacanth, powdered    | 8081201      | 1              |
| Caelo           | Tragacanth, powdered    | 14162205     | 5              |
| Caelo           | Tragacanth, powdered    | 12285402     | 1              |
| Caelo           | Tragacanth, powdered    | 12285403     | 4              |
| Caelo           | Tragacanth, powdered    | 13095203     | 1              |
| Caelo           | Tragacanth, powdered    | 13095208     | 3              |
| Caelo           | Tragacanth, powdered    | 15041302     | 1              |
| Caelo           | Tragacanth, powdered    | 11128905     | 1              |
| Caelo           | Tragacanth, powdered    | 9081202      | 1              |
| Caelo           | Tragacanth, powdered    | 7021402      | 1              |
| Caelo           | Tragacanth, powdered    | 15085602     | 4              |
| Caelo           | Tragacanth, powdered    | 12108801     | 1              |
| Caelo           | Tragacanth, powdered    | 15085606     | 2              |
| Caelo           | Tragacanth, powdered    | 15041303     | 2              |
| Caelo           | Tragacanth, powdered    | 15121203     | 1              |
| Caelo           | Tricalcium phosphate    | 1056303      | 1              |
| Caelo           | Trichloroacetic acid    | 13056213     | 1              |
| Caelo           | Trichloroacetic acid    | 3071204      | 1              |
| Caelo           | Trichloroacetic acid    | 12g04m11     | 1              |
| Caelo           | Trichloroacetic acid    | 11011306     | 1              |
| Caelo           | Trichloroacetic acid    | 10379401     | 3              |
| Caelo           | Trichloroacetic acid    | 10130802     | 1              |
| Caelo           | Trichloroacetic acid    | 12135201     | 1              |
| Caelo           | Trichloroacetic acid    | 12135207     | 5              |
| Caelo           | Trichloroacetic acid    | 12135203     | 1              |
| Caelo           | Trichloroacetic acid    | 6091306      | 1              |
| Caelo           | Trichloroacetic acid    | 13056212     | 1              |
| Caelo           | Trichloroacetic acid    | 13056209     | 1              |
| Caelo           | Trichloroacetic acid    | 13056203     | 2              |
| Caelo           | Trichloroacetic acid    | 12135210     | 4              |
| Caelo           | Turmeric root, cut      | 11160405     | 1              |
| Caelo           | Turmeric root, cut      | 15207601     | 1              |
| Caelo           | Turmeric root, cut      | 15158001     | 2              |
| Caelo           | Turmeric root, cut      | 1213650      | 1              |
| Caelo           | Turmeric root, cut      | 12136506     | 2              |
| Caelo           | Turmeric root, cut      | 12136501     | 2              |
| Caelo           | Turmeric root, cut      | 12136505     | 1              |
| Caelo           | Turmeric root, cut      | 12136503     | 2              |
| Caelo           | Turmeric root, cut      | 12136507     | 1              |
| Caelo           | Turmeric root, cut      | 13360204     | 2              |
| Caelo           | Turmeric root, cut      | 15372603     | 1              |
| Caelo           | Turmeric root, cut      | 12136504     | 2              |
| Caelo           | Turmeric root, cut      | 15158001     | 2              |
| Caelo           | Turmeric, javanese, cut | 14017706     | 1              |
| Caelo           | Turmeric, javanese, cut | 13262903     | 1              |
| Caelo           | Turmeric, javanese, cut | 12319206     | 3              |
| Caelo           | Turmeric, javanese, cut | 13262907     | 1              |
| Caelo           | Turmeric, javanese, cut | 11046305     | 1              |
| Caelo           | Turmeric, javanese, cut | 15120202     | 2              |
| Caelo           | Turmeric, javanese, cut | 14309503     | 1              |
| Caelo           | Turmeric, javanese, cut | 12319201     | 1              |
| Caelo           | Turmeric, javanese, cut | 25041313     | 1              |
| Caelo           | Turmeric, javanese, cut | 12319206     | 2              |
| Caelo           | Turmeric, javanese, cut | 11182903     | 1              |

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| Supplier | Substance               | Batch               | Spectra |
|----------|-------------------------|---------------------|---------|
| Caelo    | Valerian root, cut      | 1319002             | 1       |
| Caelo    | Valerian root, cut      | 12033810            | 1       |
| Caelo    | Valerian root, cut      | 12033808            | 7       |
| Caelo    | Valerian root, cut      | 12033807            | 1       |
| Caelo    | Valerian root, cut      | 12033806            | 1       |
| Caelo    | Valerian root, cut      | 12033805            | 5       |
| Caelo    | Valerian root, cut      | 120338012           | 1       |
| Caelo    | Valerian root, cut      | 13119004            | 3       |
| Caelo    | Valerian root, cut      | 11103612            | 4       |
| Caelo    | Valerian root, cut      | 11103611            | 1       |
| Caelo    | Valerian root, cut      | 11035002            | 1       |
| Caelo    | Valerian root, cut      | 3091202             | 1       |
| Caelo    | Valerian root, cut      | 11349101            | 5       |
| Caelo    | Valerian root, cut      | 11103608            | 1       |
| Caelo    | Valerian root, cut      | 11103607            | 6       |
| Caelo    | Valerian root, cut      | 11103606            | 1       |
| Caelo    | Valerian root, cut      | 11103602            | 2       |
| Caelo    | Valerian root, cut      | 11103601            | 2       |
| Caelo    | Valerian root, cut      | 13196801-3564412081 | 1       |
| Caelo    | Valerian root, cut      | 12033811            | 6       |
| Caelo    | Valerian root, cut      | 12033812            | 11      |
| Caelo    | Valerian root, cut      | 1328                | 1       |
| Caelo    | Valerian root, cut      | 1203812             | 1       |
| Caelo    | Valerian root, cut      | 20081303            | 1       |
| Caelo    | Valerian root, cut      | 15175208            | 2       |
| Caelo    | Valerian root, cut      | 15175205            | 1       |
| Caelo    | Valerian root, cut      | 15175202            | 2       |
| Caelo    | Valerian root, cut      | 14179404            | 3       |
| Caelo    | Valerian root, cut      | 14179403            | 1       |
| Caelo    | Valerian root, cut      | 13287402            | 3       |
| Caelo    | Valerian root, cut      | 13119003            | 14      |
| Caelo    | Valerian root, cut      | 13196806            | 6       |
| Caelo    | Valerian root, cut      | 13119002            | 20      |
| Caelo    | Valerian root, cut      | 1203804             | 1       |
| Caelo    | Valerian root, cut      | 13196805            | 1       |
| Caelo    | Valerian root, cut      | 13196802            | 6       |
| Caelo    | Valerian root, cut      | 2712A-02167         | 1       |
| Caelo    | Valerian root, cut      | 13196801            | 1       |
| Caelo    | Valerian root, cut      | 28101303            | 1       |
| Caelo    | Valerian root, cut      | 29101303            | 1       |
| Caelo    | Valerian root, cut      | 31101202            | 1       |
| Caelo    | Valerian root, cut      | 31121201            | 1       |
| Caelo    | Valerian root, cut      | nachprüfung         | 1       |
| Caelo    | Valerian root, cut      | 13119001            | 1       |
| Caelo    | Valerian root, powdered | 13196802            | 1       |
| Caelo    | Valerian root, powdered | 13196806            | 1       |
| Caelo    | Valerian root, powdered | 13196809            | 1       |
| Caelo    | Valerian root, powdered | 13287402            | 3       |
| Caelo    | Valerian root, powdered | 15175204            | 1       |
| Caelo    | Verbena herb, cut       | 11031108            | 11      |
| Caelo    | Verbena herb, cut       | 11031106            | 7       |
| Caelo    | Verbena herb, cut       | 11031110            | 6       |
| Caelo    | Verbena herb, cut       | 11031103            | 2       |
| Caelo    | Verbena herb, cut       | 11031107            | 2       |
| Caelo    | Verbena herb, cut       | 11031105            | 3       |
| Caelo    | Verbena herb, cut       | 6111301             | 1       |
| Caelo    | Verbena herb, cut       | 13351401            | 1       |
| Caelo    | Verbena herb, cut       | 4651b120611         | 1       |
| Caelo    | Verbena herb, cut       | 3013E-01691         | 1       |
| Caelo    | Verbena herb, cut       | 2x12188202          | 1       |

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| <b>Supplier</b> | <b>Substance</b>        | <b>Batch</b>       | <b>Spectra</b> |
|-----------------|-------------------------|--------------------|----------------|
| Caelo           | Verbena herb, cut       | 19111205           | 1              |
| Caelo           | Verbena herb, cut       | 15012405           | 1              |
| Caelo           | Verbena herb, cut       | 13151003           | 5              |
| Caelo           | Verbena herb, cut       | 13151001           | 17             |
| Caelo           | Verbena herb, cut       | 12383002           | 2              |
| Caelo           | Verbena herb, cut       | 12188203           | 6              |
| Caelo           | Verbena herb, cut       | 12383005           | 1              |
| Caelo           | Verbena herb, cut       | 12187601           | 16             |
| Caelo           | Verbena herb, cut       | 12188202           | 11             |
| Caelo           | Verbena herb, cut       | 110031110          | 1              |
| Caelo           | Verbena herb, cut       | 11031101           | 1              |
| Caelo           | Verbena herb, cut       | 11031102           | 1              |
| Caelo           | Verbena herb, cut       | 10034903           | 1              |
| Caelo           | Verbena herb, cut       | 11031109           | 1              |
| Caelo           | Verbena herb, cut       | 12178601           | 1              |
| Caelo           | Walnut bark, cut        | 11016605           | 2              |
| Caelo           | Walnut bark, cut        | 11325605           | 2              |
| Caelo           | Walnut bark, cut        | 11016602           | 1              |
| Caelo           | Walnut bark, cut        | 11325606           | 2              |
| Caelo           | Walnut bark, cut        | 11325603           | 2              |
| Caelo           | Walnut bark, cut        | 11016604           | 2              |
| Caelo           | Walnut leaf, cut        | nachprüfung        | 2              |
| Caelo           | Walnut leaf, cut        | 12124603-341930192 | 1              |
| Caelo           | Walnut leaf, cut        | 11103009           | 1              |
| Caelo           | Walnut leaf, cut        | 4713U01499         | 1              |
| Caelo           | Walnut leaf, cut        | 1313M-01499        | 1              |
| Caelo           | Walnut leaf, cut        | 8071502            | 1              |
| Caelo           | Walnut leaf, cut        | 12124607           | 1              |
| Caelo           | Walnut leaf, cut        | 12124605           | 8              |
| Caelo           | Walnut leaf, cut        | 12124502           | 1              |
| Caelo           | Walnut leaf, cut        | 14064904           | 6              |
| Caelo           | Walnut leaf, cut        | 11103004           | 6              |
| Caelo           | Walnut leaf, cut        | 11103008           | 6              |
| Caelo           | Walnut leaf, cut        | 14064910           | 1              |
| Caelo           | Walnut leaf, cut        | 11103007           | 8              |
| Caelo           | Walnut leaf, cut        | 11103003           | 3              |
| Caelo           | Walnut leaf, cut        | 10050413           | 1              |
| Caelo           | Walnut leaf, cut        | 1214603            | 1              |
| Caelo           | Walnut leaf, cut        | 14064906           | 4              |
| Caelo           | Walnut leaf, cut        | 14064909           | 2              |
| Caelo           | Walnut leaf, cut        | 1414Q01499         | 1              |
| Caelo           | Walnut leaf, cut        | 14064902           | 3              |
| Caelo           | Walnut leaf, cut        | 14064903           | 1              |
| Caelo           | Walnut leaf, cut        | 15126003           | 5              |
| Caelo           | Walnut leaf, cut        | 25041404           | 1              |
| Caelo           | Walnut leaf, cut        | 3712Q-01499        | 1              |
| Caelo           | Walnut leaf, cut        | 15126004           | 1              |
| Caelo           | Walnut leaf, cut        | 15126008           | 2              |
| Caelo           | Walnut leaf, cut        | 3051301            | 1              |
| Caelo           | Walnut leaf, cut        | 414Q1499           | 1              |
| Caelo           | Walnut leaf, cut        | 11103001           | 2              |
| Caelo           | Walnut leaf, cut        | 11103002           | 1              |
| Caelo           | Walnut leaf, cut        | 11103005           | 1              |
| Caelo           | Walnut leaf, cut        | 11103010           | 6              |
| Caelo           | Walnut leaf, cut        | 12124601           | 7              |
| Caelo           | Walnut leaf, cut        | 12124602           | 3              |
| Caelo           | Walnut leaf, cut        | 15126002           | 1              |
| Caelo           | White deadnettle flower | 11371613           | 2              |
| Caelo           | White deadnettle flower | 11371609           | 3              |
| Caelo           | White deadnettle flower | 11371611           | 2              |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | White deadnettle flower  | 12275802            | 1       |
| Caelo    | White deadnettle flower  | 2101301             | 1       |
| Caelo    | White deadnettle flower  | 10081206            | 1       |
| Caelo    | White deadnettle flower  | 11371608            | 1       |
| Caelo    | White deadnettle flower  | 11371610            | 5       |
| Caelo    | White deadnettle flower  | 12152402            | 2       |
| Caelo    | White deadnettle flower  | 15299101            | 1       |
| Caelo    | White deadnettle flower  | 52470437            | 1       |
| Caelo    | White deadnettle flower  | 9231005             | 1       |
| Caelo    | White deadnettle flower  | 11371604            | 1       |
| Caelo    | White deadnettle herb... | pzn4269354          | 1       |
| Caelo    | White deadnettle herb... | 11371711            | 2       |
| Caelo    | White deadnettle herb... | 11371709            | 1       |
| Caelo    | White deadnettle herb... | 11371708            | 5       |
| Caelo    | White deadnettle herb... | 11371707            | 1       |
| Caelo    | White deadnettle herb... | 11371701            | 1       |
| Caelo    | White deadnettle herb... | 11371705            | 1       |
| Caelo    | White deadnettle herb... | 1137170301-15       | 1       |
| Caelo    | White deadnettle herb... | 11371703            | 1       |
| Caelo    | White deadnettle herb... | 11371702            | 1       |
| Caelo    | White deadnettle herb... | 11371706            | 3       |
| Caelo    | White deadnettle herb... | 11371712            | 1       |
| Caelo    | White mustard seed, p... | 13224804            | 3       |
| Caelo    | White mustard seed, p... | 12375706            | 2       |
| Caelo    | White mustard seed, p... | 13224801            | 1       |
| Caelo    | White mustard seed, p... | 12375701            | 1       |
| Caelo    | White mustard seed, p... | 12375704            | 1       |
| Caelo    | White mustard seed, p... | 12375705            | 1       |
| Caelo    | White mustard seed, p... | 12375705            | 4       |
| Caelo    | White mustard seed, p... | 7254a110823         | 1       |
| Caelo    | White mustard seed, p... | 12375702            | 1       |
| Caelo    | Wild apple, sweet        | 11229805            | 1       |
| Caelo    | Wild pansy, cut          | 15021301            | 1       |
| Caelo    | Wild pansy, cut          | 17101205            | 1       |
| Caelo    | Wild pansy, cut          | 14061311            | 1       |
| Caelo    | Wild pansy, cut          | 12189204-3458312120 | 1       |
| Caelo    | Wild pansy, cut          | 13091205            | 1       |
| Caelo    | Wild pansy, cut          | 14312904            | 1       |
| Caelo    | Wild pansy, cut          | 12189204-3463312101 | 1       |
| Caelo    | Wild pansy, cut          | 1289203             | 1       |
| Caelo    | Wild pansy, cut          | 12382806            | 1       |
| Caelo    | Wild pansy, cut          | 12189204            | 5       |
| Caelo    | Wild pansy, cut          | 12189204            | 10      |
| Caelo    | Wild pansy, cut          | 12189203            | 6       |
| Caelo    | Wild pansy, cut          | 11216103            | 2       |
| Caelo    | Wild pansy, cut          | 10291009            | 4       |
| Caelo    | Wild pansy, cut          | 10291008            | 1       |
| Caelo    | Wild pansy, cut          | 10291007            | 1       |
| Caelo    | Wild pansy, cut          | 5021304             | 1       |
| Caelo    | Wild pansy, cut          | 7101303             | 1       |
| Caelo    | Wild pansy, cut          | 12382802            | 1       |
| Caelo    | Wild pansy, cut          | 12382805            | 1       |
| Caelo    | Wild pansy, cut          | 12189203            | 4       |
| Caelo    | Wild thyme, cut          | 111374807           | 1       |
| Caelo    | Wild thyme, cut          | 11031203            | 1       |
| Caelo    | Wild thyme, cut          | 11374803            | 2       |
| Caelo    | Wild thyme, cut          | 11374805            | 5       |
| Caelo    | Wild thyme, cut          | 11374805i.0.        | 1       |
| Caelo    | Wild thyme, cut          | 13086801            | 1       |
| Caelo    | Wild thyme, cut          | 13086805            | 3       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>        | <b>Spectra</b> |
|-----------------|--------------------------|---------------------|----------------|
| Caelo           | Wild thyme, cut          | 4501A120813         | 2              |
| Caelo           | Willow bark, cut         | 2185206             | 1              |
| Caelo           | Willow bark, cut         | 21011302            | 1              |
| Caelo           | Willow bark, cut         | 13180705            | 1              |
| Caelo           | Willow bark, cut         | 13180701            | 1              |
| Caelo           | Willow bark, cut         | 12185210            | 1              |
| Caelo           | Willow bark, cut         | 12185207            | 3              |
| Caelo           | Willow bark, cut         | 12185204            | 5              |
| Caelo           | Willow bark, cut         | 12185206            | 5              |
| Caelo           | Willow bark, cut         | 12185202            | 2              |
| Caelo           | Willow bark, cut         | 272101              | 1              |
| Caelo           | Willow bark, cut         | 12185201            | 6              |
| Caelo           | Willow bark, cut         | 11073210            | 4              |
| Caelo           | Willow bark, cut         | 11073208            | 1              |
| Caelo           | Willow bark, cut         | 11073201            | 1              |
| Caelo           | Willow bark, cut         | 9071301             | 1              |
| Caelo           | Willow bark, cut         | 12185208            | 15             |
| Caelo           | Willow bark, cut         | 13180702            | 4              |
| Caelo           | Willow bark, cut         | 13180705-3530411072 | 1              |
| Caelo           | Willow bark, cut         | 4312E-01305         | 1              |
| Caelo           | Willow herb, cut         | 13200203            | 1              |
| Caelo           | Willow herb, cut         | 11347318            | 2              |
| Caelo           | Willow herb, cut         | 11347316            | 1              |
| Caelo           | Willow herb, cut         | 11347311            | 1              |
| Caelo           | Willow herb, cut         | 10194216            | 1              |
| Caelo           | Willow herb, cut         | 13104702            | 1              |
| Caelo           | Willowherb, small flo... | 13200202-3481312102 | 1              |
| Caelo           | Willowherb, small flo... | 12117701-3371319012 | 1              |
| Caelo           | Willowherb, small flo... | 10326108            | 15             |
| Caelo           | Willowherb, small flo... | 2081305             | 1              |
| Caelo           | Willowherb, small flo... | 412041              | 1              |
| Caelo           | Willowherb, small flo... | 31101303            | 1              |
| Caelo           | Willowherb, small flo... | 29121201            | 1              |
| Caelo           | Willowherb, small flo... | 28031318            | 1              |
| Caelo           | Willowherb, small flo... | 2412E-01641         | 1              |
| Caelo           | Willowherb, small flo... | 22011304            | 1              |
| Caelo           | Willowherb, small flo... | 21061307            | 1              |
| Caelo           | Willowherb, small flo... | 18031305            | 1              |
| Caelo           | Willowherb, small flo... | 16081304            | 1              |
| Caelo           | Willowherb, small flo... | 16081302            | 1              |
| Caelo           | Willowherb, small flo... | 15101302            | 1              |
| Caelo           | Willowherb, small flo... | 14267909            | 1              |
| Caelo           | Willowherb, small flo... | 13355906            | 2              |
| Caelo           | Willowherb, small flo... | 13200203            | 9              |
| Caelo           | Willowherb, small flo... | 1031301             | 1              |
| Caelo           | Willowherb, small flo... | 15011411            | 1              |
| Caelo           | Willowherb, small flo... | 13071301            | 1              |
| Caelo           | Willowherb, small flo... | 613M-01641          | 1              |
| Caelo           | Willowherb, small flo... | 7071201             | 1              |
| Caelo           | Willowherb, small flo... | 9378908             | 1              |
| Caelo           | Willowherb, small flo... | 10326104            | 5              |
| Caelo           | Willowherb, small flo... | 10326107            | 1              |
| Caelo           | Willowherb, small flo... | 10326109            | 3              |
| Caelo           | Willowherb, small flo... | 12041301            | 1              |
| Caelo           | Willowherb, small flo... | 13200201            | 4              |
| Caelo           | Willowherb, small flo... | 12117701            | 8              |
| Caelo           | Willowherb, small flo... | 12064506            | 1              |
| Caelo           | Wormwood herb, cut       | 12355804            | 9              |
| Caelo           | Wormwood herb, cut       | 13387008            | 1              |
| Caelo           | Wormwood herb, cut       | 13381905            | 2              |

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| Supplier | Substance             | Batch       | Spectra |
|----------|-----------------------|-------------|---------|
| Caelo    | Wormwood herb, cut    | 13174403    | 1       |
| Caelo    | Wormwood herb, cut    | 1911E-01611 | 1       |
| Caelo    | Wormwood herb, cut    | 2213M-01611 | 1       |
| Caelo    | Wormwood herb, cut    | 7031301     | 1       |
| Caelo    | Wormwood herb, cut    | 13174402    | 1       |
| Caelo    | Wormwood herb, cut    | 11285811    | 4       |
| Caelo    | Wormwood herb, cut    | 6101203     | 1       |
| Caelo    | Wormwood herb, cut    | 12355807    | 10      |
| Caelo    | Wormwood herb, cut    | 12355808    | 2       |
| Caelo    | Wormwood herb, cut    | 11285809    | 1       |
| Caelo    | Wormwood herb, cut    | 7011401     | 1       |
| Caelo    | Wormwood herb, cut    | 15408304    | 1       |
| Caelo    | Wormwood herb, cut    | 11285805    | 4       |
| Caelo    | Wormwood herb, cut    | 12355805    | 5       |
| Caelo    | Wormwood herb, cut    | 11285804    | 1       |
| Caelo    | Wormwood herb, cut    | nachprüfung | 1       |
| Caelo    | Wormwood herb, cut    | 277513      | 2       |
| Caelo    | Wormwood herb, cut    | 11285803    | 3       |
| Caelo    | Wormwood herb, cut    | 11285806    | 2       |
| Caelo    | Wormwood herb, cut    | 12103003    | 12      |
| Caelo    | Wormwood herb, cut    | 12355803    | 36      |
| Caelo    | Wormwood herb, cut    | 13174401    | 3       |
| Caelo    | Wormwood herb, cut    | 12355802    | 4       |
| Caelo    | Wormwood herb, cut    | 12355801    | 24      |
| Caelo    | Wormwood herb, cut    | 13381902    | 4       |
| Caelo    | Wormwood herb, cut    | 272957      | 3       |
| Caelo    | Wormwood herb, cut    | 11285802    | 3       |
| Caelo    | Wormwood herb, cut    | 1108508     | 1       |
| Caelo    | Yarrow flower, rubbed | 12363002    | 6       |
| Caelo    | Yarrow flower, rubbed | 12363007    | 1       |
| Caelo    | Yarrow flower, rubbed | 13350507    | 1       |
| Caelo    | Yarrow flower, rubbed | 70139427    | 1       |
| Caelo    | Yarrow flower, rubbed | 12338306    | 1       |
| Caelo    | Yarrow flower, rubbed | 12363005    | 6       |
| Caelo    | Yarrow flower, rubbed | 12267703    | 3       |
| Caelo    | Yarrow herb, cut      | 14018503    | 2       |
| Caelo    | Yarrow herb, cut      | 13381810    | 1       |
| Caelo    | Yarrow herb, cut      | 13381806    | 3       |
| Caelo    | Yarrow herb, cut      | 1309106     | 1       |
| Caelo    | Yarrow herb, cut      | 13381804    | 3       |
| Caelo    | Yarrow herb, cut      | 130929105   | 1       |
| Caelo    | Yarrow herb, cut      | 3313Q-01665 | 1       |
| Caelo    | Yarrow herb, cut      | 13381805    | 1       |
| Caelo    | Yarrow herb, cut      | 14018508    | 1       |
| Caelo    | Yarrow herb, cut      | 1408510     | 1       |
| Caelo    | Yarrow herb, cut      | 14018516    | 1       |
| Caelo    | Yarrow herb, cut      | 15006708    | 1       |
| Caelo    | Yarrow herb, cut      | 15006713    | 1       |
| Caelo    | Yarrow herb, cut      | 29071301    | 1       |
| Caelo    | Yarrow herb, cut      | 15006720    | 1       |
| Caelo    | Yarrow herb, cut      | 16041302    | 1       |
| Caelo    | Yarrow herb, cut      | 130291103   | 1       |
| Caelo    | Yarrow herb, cut      | 16102013E   | 1       |
| Caelo    | Yarrow herb, cut      | H-220313-1  | 1       |
| Caelo    | Yarrow herb, cut      | 2311E-01665 | 1       |
| Caelo    | Yarrow herb, cut      | 27011404    | 1       |
| Caelo    | Yarrow herb, cut      | 31121207    | 1       |
| Caelo    | Yarrow herb, cut      |             | 3       |
| Caelo    | Yarrow herb, cut      | 11280517    | 2       |
| Caelo    | Yarrow herb, cut      | 10101205    | 1       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Caelo    | Yarrow herb, cut         | 11280511            | 6       |
| Caelo    | Yarrow herb, cut         | 13029108            | 9       |
| Caelo    | Yarrow herb, cut         | 10081301            | 1       |
| Caelo    | Yarrow herb, cut         | 9121304             | 1       |
| Caelo    | Yarrow herb, cut         | 9101311             | 1       |
| Caelo    | Yarrow herb, cut         | 8011421             | 1       |
| Caelo    | Yarrow herb, cut         | 11280512            | 10      |
| Caelo    | Yarrow herb, cut         | 5021302             | 1       |
| Caelo    | Yarrow herb, cut         | 12379602            | 19      |
| Caelo    | Yarrow herb, cut         | 11218404            | 2       |
| Caelo    | Yarrow herb, cut         | 12338306-3358319071 | 1       |
| Caelo    | Yarrow herb, cut         | 12338311            | 3       |
| Caelo    | Yarrow herb, cut         | 13029107-3418310182 | 1       |
| Caelo    | Yarrow herb, cut         | 13029107-3436311151 | 1       |
| Caelo    | Yarrow herb, cut         | 11280503            | 1       |
| Caelo    | Yarrow herb, cut         | 11306301            | 1       |
| Caelo    | Yarrow herb, cut         | 12338303            | 10      |
| Caelo    | Yarrow herb, cut         | 12379606            | 12      |
| Caelo    | Yarrow herb, cut         | 13029105            | 4       |
| Caelo    | Yarrow herb, cut         | 11306303            | 2       |
| Caelo    | Yarrow herb, cut         | 13029106            | 12      |
| Caelo    | Yarrow herb, cut         | 12379607            | 1       |
| Caelo    | Yarrow herb, cut         | 12379603            | 7       |
| Caelo    | Yarrow herb, cut         | 12379601            | 11      |
| Caelo    | Yarrow herb, cut         | 12338306            | 5       |
| Caelo    | Yarrow herb, cut         | 13029104            | 4       |
| Caelo    | Yarrow herb, cut         | 12338304            | 19      |
| Caelo    | Yarrow herb, cut         | 12336306            | 1       |
| Caelo    | Yarrow herb, cut         | 12041302            | 1       |
| Caelo    | Yarrow herb, cut         | 13029107            | 2       |
| Caelo    | Yarrow herb, cut         | 11306304            | 1       |
| Caelo    | Yarrow herb, cut         | 12338305            | 12      |
| Caelo    | Yellow chaste weed, cut  | 15029505            | 1       |
| Caelo    | Yellow chaste weed, cut  | 10244408            | 1       |
| Caelo    | Yellow chaste weed, cut  | 10244407            | 1       |
| Caelo    | Yellow chaste weed, cut  | 1024407             | 1       |
| Caelo    | Yellow chaste weed, cut  | 512U-01473          | 1       |
| Caelo    | Yellow chaste weed, cut  | 12170603            | 1       |
| Caelo    | Yellow chaste weed, cut  | 12170605            | 2       |
| Caelo    | Yellow chaste weed, cut  | 11293101            | 5       |
| Caelo    | Yellow chaste weed, cut  | 12170602            | 2       |
| Caelo    | Zedoary root, cut        | 11091607            | 1       |
| Caelo    | Zedoary root, cut        | 111091607           | 1       |
| Caelo    | Zedoary root, cut        | 25111304            | 1       |
| Caelo    | Zedoary root, cut        | 13010102            | 6       |
| Caelo    | Zedoary root, cut        | 12125304            | 2       |
| Caelo    | Zedoary root, cut        | 12125303            | 1       |
| Caelo    | Zedoary root, cut        | 13010106            | 4       |
| Caelo    | Zedoary root, cut        | 11091603            | 1       |
| Caelo    | Zedoary root, cut        | 11091604            | 1       |
| Caelo    | Zedoary root, cut        | nachprüfung         | 1       |
| Caelo    | Zedoary root, powdered   | 12007504            | 1       |
| Caelo    | Zedoary root, powdered   | 13165501            | 2       |
| Caelo    | Zedoary root, powdered   | 12344605            | 1       |
| Caelo    | Zedoary root, powdered   | 13165504            | 4       |
| Caelo    | Zedoary root, powdered   | 15277101            | 1       |
| Caelo    | Zinc sulfate heptahyd... | 12257816            | 1       |
| Caelo    | Zinc sulfate heptahyd... | CH:001/0913         | 1       |
| Caelo    | Zinc sulfate heptahyd... | 81554199            | 1       |
| Caelo    | Zinc sulfate heptahyd... | 4012Q-02798         | 1       |

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| Supplier                 | Substance                | Batch       | Spectra |
|--------------------------|--------------------------|-------------|---------|
| Caelo                    | Zinc sulfate heptahyd... | 12257818    | 1       |
| Caelo                    | Zinc sulfate heptahyd... | 12257809    | 3       |
| Caelo                    | Zinc sulfate heptahyd... | 12257802    | 1       |
| Caelo                    | Zinc sulfate heptahyd... | 11095621    | 1       |
| Caelo                    | Zinc sulfate heptahyd... | 11095601    | 1       |
| Caelo                    | Zinc sulfate heptahyd... | 110500201   | 1       |
| Caesar & Lorenz          | Caraway fruit            | 12226609    | 5       |
| Caesar & Lorenz          | Yarrow herb, cut         | 12379605    | 4       |
| Caesar & Loretz          | Kaolin, heavy            | 13041801    | 4       |
| Caesar & Loretz GmbH     | Hawthorn flower          | 11068206    | 5       |
| Caesar & Loretz GmbH     | Magnesium chloride he... | 13064223    | 1       |
| Caesar & Loretz GmbH     | Morphine hydrochloride   | 15199711    | 1       |
| Caesar & Loretz GmbH     | Morphine hydrochloride   | 15199712    | 1       |
| Caesar & Loretz GmbH     | Morphine hydrochloride   | 15199711(2) | 1       |
| Caesar & Loretz GmbH     | Morphine hydrochloride   | 15199711(1) | 1       |
| Caesar & Loretz GmbH ... | Bitter fennel            | 11016319    | 4       |
| Caesar & Loretz GmbH ... | Black mustard seed, p... | 11276701    | 3       |
| Caesar & Loretz GmbH ... | Liquorice root, peeled   | 11034014    | 4       |
| Caesar & Loretz GmbH ... | Mallow flower, cut       | 10357901    | 2       |
| Caesar & Loretz GmbH ... | Nettle leaf, cut         | 10291405    | 3       |
| Caesar & Loretz GmbH ... | Raspberry leaf, cut      | 10013408    | 3       |
| Caesar & Loretz GmbH ... | Ribwort plantain, cut    | 10315707    | 5       |
| Caesar & Loretz GmbH ... | Sage leaf, cut           | 11056109    | 8       |
| Caesar & Loretz GmbH ... | Senna leaf, cut          | 11041012    | 1       |
| Caesar & Loretz GmbH ... | Senna leaf, cut          | 11277303    | 6       |
| Caesar & Loretz GmbH ... | Senna pods, tinnevelly   | 11003003    | 1       |
| Caesar & Loretz GmbH ... | Potassium hydroxide      | 12057902    | 2       |
| Caesar & Loretz GmbH ... | Sage leaf, cut           | 11056121    | 4       |
| Caesar & Loretz GmbH ... | Black cummin seed        | LMV1505024  | 1       |
| Caesar & Loretz GmbH,... | Aluminium chloride he... | 12047508    | 5       |
| Caesar & Loretz GmbH,... | Aniseed                  | 12226402    | 5       |
| Caesar & Loretz GmbH,... | Bitter fennel            | 12094711    | 3       |
| Caesar & Loretz GmbH,... | Bitter fennel            | 12094705    | 5       |
| Caesar & Loretz GmbH,... | Bitter fennel            | 12094705    | 3       |
| Caesar & Loretz GmbH,... | Bitter fennel            | 12094707    | 8       |
| Caesar & Loretz GmbH,... | Caraway fruit            | 11003213    | 2       |
| Caesar & Loretz GmbH,... | Caraway fruit            | 9267824     | 2       |
| Caesar & Loretz GmbH,... | Equisetum stem, cut      | 11207010    | 1       |
| Caesar & Loretz GmbH,... | Gentian root, cut        | 12244603    | 2       |
| Caesar & Loretz GmbH,... | Maté leaf, cut           | 13118002    | 9       |
| Caesar & Loretz GmbH,... | Nettle leaf, cut         | 10291423    | 9       |
| Caesar & Loretz GmbH,... | Sage leaf, cut           | 12370016    | 8       |
| Caesar & Loretz GmbH,... | Sage leaf, cut           | 12370010    | 18      |
| Caesar & Loretz GmbH,... | Sage leaf, cut           | 12370002    | 4       |
| Caesar & Loretz GmbH,... | Sage leaf, cut           | 11347502    | 6       |
| Caesar & Loretz GmbH,... | Senna leaf, cut          | 12273103    | 15      |
| Caesar & Loretz GmbH,... | Senna leaf, cut          | 11277308    | 3       |
| Caesar & Loretz GmbH,... | Senna leaf, cut          | 11277314    | 5       |
| Caesar & Loretz GmbH,... | Senna leaf, cut          | 13136708    | 7       |
| Caesar & Loretz GmbH,... | Senna pods, tinnevelly   | 11003012    | 1       |
| Caesar & Loretz GmbH,... | Senna pods, tinnevelly   | 11003014    | 1       |
| Caesar & Loretz GmbH,... | Senna pods, tinnevelly   | 12267601    | 2       |
| Caesar & Loretz GmbH,... | Senna pods, tinnevelly   | 12267603    | 1       |
| Caesar & Loretz GmbH,... | Sodium hydrogen carbo... | 13060102    | 4       |
| Caesar & Loretz GmbH,... | Tall golden rod, cut     | 11207014    | 3       |
| Caesar & Loretz GmbH,... | Wild thyme, cut          | 11374802    | 1       |
| Caesar & Loretz/ Noweda  | Heavy alkaline bismut... | 12145701    | 1       |
| Caesar & Loretz/ Noweda  | Hyssop herb, cut         | 11374301    | 1       |
| Caesar & Loretz/ Noweda  | Ivy leaf, cut            | 12225606    | 5       |
| Caesar & Loretz/Noweda   | Aniseed                  | 153986002   | 1       |

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| Supplier                 | Substance                | Batch         | Spectra |
|--------------------------|--------------------------|---------------|---------|
| Caesar & Loretz/Noweda   | Caraway fruit            | 15056601      | 1       |
| Caesar&Loretz GmbH D-... | Senna leaf, cut          | 12115504      | 5       |
| Caesar&loretz,AHC        | Nystatin                 | 14196509      | 2       |
| Caesar&loretz,Anzag      | Nystatin                 | 12158008      | 10      |
| Caesar&loretz,Phoenix    | Frangula bark, cut       | 14163104      | 1       |
| Caesar&loretz,Phoenix    | Ladys bedstraw herb,...  | 14019215      | 1       |
| Caesar&loretz,Phoenix    | Ladys bedstraw herb,...  | 14019206      | 1       |
| Caesar&loretz,Phoenix    | Marjoram herb, rubbed    | 14181005      | 1       |
| Caesar&loretz,Phoenix    | Nystatin                 | 1111057-01    | 13      |
| Caesar&loretz,Phoenix    | Nystatin                 | 1218008       | 1       |
| Caesar&loretz,Phoenix    | Nystatin                 | 13173408      | 2       |
| Caesar&loretz,Phoenix    | Nystatin                 | 14363512      | 2       |
| caesar&loretz,Phönix     | Iceland moss, cut        | 14304404      | 2       |
| Caesar/ Noweda           | Black mustard seed, p... | 14293711      | 3       |
| Caesar/Lorenz            | Matricaria flower        | 12337610      | 2       |
| Caesar/Noweda            | Aloes, cape, cut         | 2013E-01089   | 1       |
| Caesar/Noweda            | Aloes, cape, cut         | 12338211      | 1       |
| Caesar/Noweda            | Aluminium potassium s... | 12184411      | 2       |
| Caesar/Noweda            | American liverwort, cut  | 11254608      | 1       |
| Caesar/Noweda            | Bogbean leaf, cut        | 1510U-01517   | 1       |
| Caesar/Noweda            | Coriander                | 2010M-01539   | 1       |
| Caesar/Noweda            | Couch grass rhizome, ... | 12186813      | 6       |
| Caesar/Noweda            | Elder flower, rubbed     | 4910A-01471   | 1       |
| Caesar/Noweda            | Heather, cut             | 4911I-03224   | 1       |
| Caesar/Noweda            | Ispaghula seed           | 12276509      | 3       |
| Caesar/Noweda            | Ispaghula seed           | 12276503      | 1       |
| Caesar/Noweda            | Ispaghula seed           | 12276516      | 1       |
| Caesar/Noweda            | Lycopodium herb, cut     | 1255008       | 1       |
| Caesar/Noweda            | Mullein flower, cut      | 2810E-01475   | 1       |
| Caesar/Noweda            | Psyllium seed            | 11185817      | 3       |
| Caesar/Noweda            | Psyllium seed            | 12276501      | 3       |
| Caesar/Noweda            | Restharrow root, cut     | 71015/3       | 2       |
| Caesar/Noweda            | Theriac, powdered        | 12289309      | 1       |
| caesar&loretz, 09.11.... | Podophyllum resin (fr... | 11085813      | 1       |
| Caleo/ Anzag             | Wormwood herb, cut       | 11285810      | 7       |
| calo                     | Lycopodium herb, cut     | 11255006      | 1       |
| carotech                 | Tocomax 20%              | A3_200003_1/5 | 1       |
| Cealo                    | Calcium hydrogen phos... | 12212811      | 4       |
| Cealo                    | Ispaghula seed           | 12276502      | 5       |
| Cealo                    | Magnesium chloride he... | 112354615     | 1       |
| Cealo                    | Magnesium chloride he... | 11354615      | 1       |
| Cealo                    | Ribwort plantain, cut    | 12362907      | 4       |
| celo                     | Ladys bedstraw herb,...  | nachprüfung   | 1       |
| celo                     | Tall nasturtium herb,... | nachprüfung   | 1       |
| celo                     | Yarrow herb, cut         | nachprüfung   | 1       |
| Celo                     | Agrimony, cut            | 11374003      | 1       |
| Changsha staherb natu... | Amygdalin                | STA-13032202  | 1       |
| Chiesi/Phönix            | Black cumin seed         | 14359906      | 3       |
| China Medica             | Raspberry leaf, cut      | 13086703      | 1       |
| china medica 14.06.2013  | Angelica root            | 98019         | 1       |
| china medica 14.06.2013  | Cinnamon rods (Ceylon... | 210810        | 1       |
| china medica 14.06.2013  | Cinnamon, cut            | 210842        | 1       |
| china medica 14.06.2013  | Lemon peel, cut          | 101201H045    | 1       |
| china medica 14.06.2013  | Rhubarb, cut             | 20072         | 1       |
| china medica 14.06.2013  | Water plantain rhizom... | 30065         | 1       |
| Clariant - Mindel-Food   | Bentonite                | 1301          | 1       |
| Creapure                 | Creatine                 | 515941        | 1       |
| Defektur                 | Bitter fennel            | 7/13          | 1       |
| Defektur                 | Bitter fennel            | 26813035/12   | 1       |
| Defektur                 | Bitter fennel            | 52/13         | 1       |

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| Supplier           | Substance                | Batch                | Spectra |
|--------------------|--------------------------|----------------------|---------|
| Defektur           | Bitter fennel            | 57/13                | 1       |
| Defektur           | Matricaria flower        | 10/13                | 1       |
| Defektur           | Matricaria flower        | 59/13                | 1       |
| Defektur           | Matricaria flower        | 56/12                | 1       |
| Defektur           | Matricaria flower        | 29/13                | 1       |
| Degussa / falcento | Creatine                 | 422031               | 1       |
| Denk               | D-(+)-mannose            | R-4680               | 1       |
| Dermapharm         | 8-quinolinol sulfate ... | 120905               | 1       |
| Dermapharm         | 8-quinolinol sulfate ... | 140804               | 1       |
| Dermapharm         | 8-quinolinol sulfate ... | 100804               | 1       |
| Dr. Behr           | Dimercaptosuccinic acid  | WE14020002           | 1       |
| Dr. Behr GmbH      | Dimercaptosuccinic acid  | WE14070074(003)/14G  | 1       |
| Dr. Behr GmbH      | Glucosamine sulfate 2... | 4121205              | 1       |
| Dr. Behr GmbH      | Dimercaptosuccinic acid  | WE15060032/D1/150500 | 1       |
| ebert u.jacobi     | Marian thistle fruit     | 287527               | 1       |
| Ebert-Jacobi       | Methadone hydrochloride  | 16135306             | 1       |
| Erfurter Ölmühle   | Linseed                  |                      | 1       |
| Erika apotheke     | Fumitory, cut            | 11101412             | 1       |
| Erika apotheke     | Marian thistle fruit     | 11126704             | 3       |
| Erika apotheke     | Nettle leaf, cut         | 12195001             | 11      |
| Erika apotheke     | Nettle leaf, cut         | 12184003             | 24      |
| Eu Rho             | Sodium hydrogen carbo... | 1203030-01           | 13      |
| EuRho              | Aluminium chloride he... | 1106017-01           | 2       |
| EuRho              | Aluminium chloride he... | 2512I01095           | 1       |
| EuRho              | Aluminium chloride he... | d024a                | 1       |
| EuRho              | Dithranole               | 1203025-01           | 1       |
| EuRho              | Magnesium sulfate hep... | 3512M-01835          | 1       |
| EuRho              | Sodium sulfate decahy... | 1210005-01           | 3       |
| EuRho              | Tricalcium phosphate     | 13031203             | 1       |
| Eurho/Noweda       | Black mustard seed, p... | 13356304             | 1       |
| Eurho/Phoenix      | Midazolam hydrochloride  | 12L17-N10            | 1       |
| euro               | Sodium hydrogen carbo... | 110902901            | 1       |
| Euro / Jenne       | Magnesium sulfate hep... | 1401029-01           | 2       |
| Euro OTC           | Aluminium chloride he... | 1106017-02           | 3       |
| Euro OTC           | Aluminium chloride he... | 1109025-02           | 5       |
| Euro OTC           | Aluminium chloride he... | co31a                | 1       |
| Euro OTC           | Aluminium chloride he... | 1213M-01095          | 1       |
| Euro OTC           | Aluminium chloride he... | 120402601            | 4       |
| Euro OTC           | Aluminium chloride he... | 1307011-02           | 2       |
| Euro OTC           | Aluminium chloride he... | 1307011-01           | 11      |
| Euro OTC           | Aluminium chloride he... | 120402602            | 1       |
| Euro OTC           | Aluminium chloride he... | 1210014-02-336331909 | 1       |
| Euro OTC           | Aluminium chloride he... | 1210012-01           | 1       |
| Euro OTC           | Aluminium chloride he... | 1103007-01           | 2       |
| Euro OTC           | Aluminium chloride he... | 121001401            | 4       |
| Euro OTC           | Aluminium chloride he... | 1204026-02           | 19      |
| Euro OTC           | Aluminium chloride he... | 1507002-01           | 1       |
| Euro OTC           | Aluminium chloride he... | 2111Q-01095          | 1       |
| Euro OTC           | Aluminium potassium s... | 1004046-02           | 1       |
| Euro OTC           | Ammonium chloride        | 512A-01104           | 1       |
| Euro OTC           | Ammonium chloride        | 1203029-01           | 3       |
| Euro OTC           | Ammonium chloride        | 1212017-01           | 2       |
| Euro OTC           | Ammonium chloride        | 1303029-01           | 1       |
| Euro OTC           | Amygdalin                | NF-A20130203         | 1       |
| Euro OTC           | Bentonite                | 1304026-01           | 1       |
| Euro OTC           | Betaine hydrochloride    | 1202008-01           | 1       |
| Euro OTC           | Betaine hydrochloride    | L1510011-03          | 2       |
| Euro OTC           | Betaine hydrochloride    | L1412019-01          | 1       |
| Euro OTC           | Betaine hydrochloride    | 1305027-01           | 2       |
| Euro OTC           | Betaine hydrochloride    | 1510011-02           | 1       |

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| Supplier | Substance                | Batch        | Spectra |
|----------|--------------------------|--------------|---------|
| Euro OTC | Centaury, cut            | 272897       | 3       |
| Euro OTC | Chromium yeast 0.2%      | L1406030-01  | 1       |
| Euro OTC | Chromium yeast 0.2%      | L1507039-01  | 1       |
| Euro OTC | Chromium yeast 0.2%      | L1311026-01  | 1       |
| Euro OTC | Chromium yeast 0.2%      | L1502003-01  | 1       |
| Euro OTC | Chromium yeast 0.2%      | 1303028-01   | 1       |
| Euro OTC | Chromium yeast 0.2%      | 1406030-01   | 1       |
| Euro OTC | Copper orotate dihydr... | 1206035-01   | 2       |
| Euro OTC | Copper orotate dihydr... | 2106001Z-01  | 1       |
| Euro OTC | Curcuma extract 95%      | L1107001     | 1       |
| Euro OTC | D-(+)-mannose            | L1111005-01  | 2       |
| Euro OTC | Dandelion herb with r... | 11030312     | 6       |
| Euro OTC | Dithranole               | 1008011-01   | 1       |
| Euro OTC | Dithranole               | 1008011-02   | 4       |
| Euro OTC | Dithranole               | DT/370/2012  | 1       |
| Euro OTC | Dithranole               | 1203025-02   | 20      |
| Euro OTC | Dithranole               | 1311029-01   | 2       |
| Euro OTC | Dithranole               | 20280812-1   | 1       |
| Euro OTC | Dithranole               | B:1008011-01 | 1       |
| Euro OTC | Dithranole               | 2902060-02   | 1       |
| Euro OTC | Dithranole               | 56/11072013  | 1       |
| Euro OTC | Equisetum stem, cut      | 3831A130610  | 6       |
| Euro OTC | Frankincense             | 10349212     | 2       |
| Euro OTC | Frankincense extract ... | 1104005-01   | 1       |
| Euro OTC | Frankincense extract ... | 1104005V-04  | 2       |
| Euro OTC | Frankincense extract ... | 1112016-01   | 1       |
| Euro OTC | Glucosamine sulfate 2... | L1307010-01  | 1       |
| Euro OTC | Griffonia seed extract   | 1205027      | 1       |
| Euro OTC | Hamamelis leaf, cut      | 12164805     | 4       |
| Euro OTC | Heavy magnesium oxide    | 1012033-01   | 1       |
| Euro OTC | Heavy magnesium oxide    | 1111006-01   | 1       |
| Euro OTC | Heavy magnesium oxide    | 1205012-01   | 2       |
| Euro OTC | Heavy, basic magnesiu... | 1305024-01   | 1       |
| Euro OTC | Heavy, basic magnesiu... | 1211005-01   | 4       |
| Euro OTC | Heavy, basic magnesiu... | 1205013-02   | 1       |
| Euro OTC | Hyssop herb, cut         | nachprüfung  | 1       |
| Euro OTC | Magnesium chloride he... | 1212013-01   | 4       |
| Euro OTC | Magnesium chloride he... | 1112013-01   | 2       |
| Euro OTC | Magnesium chloride he... | 1204017-01   | 2       |
| Euro OTC | Magnesium sulfate hep... | 1211022-01   | 7       |
| Euro OTC | Magnesium sulfate hep... | 1202017-01   | 6       |
| Euro OTC | Magnesium sulfate hep... | 1306015-01   | 1       |
| Euro OTC | Magnesium sulfate hep... | 170610       | 1       |
| Euro OTC | Magnesium sulfate hep... | 1206019-01   | 7       |
| Euro OTC | Magnesium sulfate hep... | 130300801    | 2       |
| Euro OTC | Magnesium sulfate hep... | 1109023-01   | 2       |
| Euro OTC | Marian thistle herb, ... | 3701A-111207 | 1       |
| Euro OTC | Matricaria flower        | 12361702     | 7       |
| Euro OTC | Methadone hydrochloride  | 14C24-B01    | 2       |
| Euro OTC | Nettle seed              | 12131507     | 2       |
| Euro OTC | Nystatin                 | 2811032-01   | 1       |
| Euro OTC | Nystatin                 | 19500711     | 1       |
| Euro OTC | Nystatin                 | 1107046-01   | 9       |
| Euro OTC | Nystatin                 | B:1107046-01 | 1       |
| Euro OTC | Nystatin                 | 1511020-02   | 1       |
| Euro OTC | Nystatin                 | 1511020-01   | 1       |
| Euro OTC | Nystatin                 | C129440      | 1       |
| Euro OTC | Nystatin                 | C129531      | 2       |
| Euro OTC | Nystatin                 | C129854      | 1       |
| Euro OTC | Nystatin                 | 111105701    | 1       |

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| Supplier       | Substance                | Batch       | Spectra |
|----------------|--------------------------|-------------|---------|
| Euro OTC       | Nystatin                 | 130705301   | 1       |
| Euro OTC       | Nystatin                 | 1307053-01  | 8       |
| Euro OTC       | Nystatin                 | 1307053-02  | 3       |
| Euro OTC       | Nystatin                 | 1212024-02  | 19      |
| Euro OTC       | Nystatin                 | 1207009-02  | 5       |
| Euro OTC       | Nystatin                 | 121024-01   | 1       |
| Euro OTC       | Nystatin                 | 1212024-01  | 21      |
| Euro OTC       | Nystatin                 | 127009-02   | 1       |
| Euro OTC       | Nystatin                 | 4014991     | 2       |
| Euro OTC       | Nystatin                 | 110704601   | 1       |
| Euro OTC       | Nystatin                 | 121202401   | 1       |
| Euro OTC       | Oak bark, cut            |             | 1       |
| Euro OTC       | Potassium hydrocarbon... | 1204038-01  | 2       |
| Euro OTC       | Potassium hydrocarbon... | 2712008-01  | 1       |
| Euro OTC       | Potassium hydrocarbon... | 2809033-01  | 1       |
| Euro OTC       | Potassium hydrocarbon... | 4413I1728   | 1       |
| Euro OTC       | Potassium hydrocarbon... | 70913Kahyca | 1       |
| Euro OTC       | Potassium hydrocarbon... | 1202013-01  | 1       |
| Euro OTC       | Potassium hydrocarbon... | 1208010-01  | 4       |
| Euro OTC       | Sodium alginate          | 1509036-01  | 1       |
| Euro OTC       | Sodium dihydrogen pho... | 1209004-01  | 2       |
| Euro OTC       | Sodium dihydrogen pho... | 1305028-01  | 1       |
| Euro OTC       | Sodium hydrogen carbo... | 120800801   | 2       |
| Euro OTC       | Sodium hydrogen carbo... | 1304017-02  | 2       |
| Euro OTC       | Sodium hydrogen carbo... | 1104013-01  | 4       |
| Euro OTC       | Sodium hydrogen carbo... | 1012011-01  | 2       |
| Euro OTC       | Sodium hydrogen carbo... | 1109029-01  | 11      |
| Euro OTC       | Sodium hydrogen carbo... | 1304017-01  | 5       |
| Euro OTC       | Sodium hydrogen carbo... | 120303001   | 1       |
| Euro OTC       | Sodium hydrogen carbo... | 1203030-02  | 9       |
| Euro OTC       | Sodium molybdate dihy... | 180910      | 1       |
| Euro OTC       | Sodium molybdate dihy... | L1305049-01 | 2       |
| Euro OTC       | Sodium molybdate dihy... | L1204020-01 | 1       |
| Euro OTC       | Sodium sulfate decahy... | 121000502   | 2       |
| Euro OTC       | Sodium sulfate decahy... | 1108035-02  | 4       |
| Euro OTC       | Sodium sulfate decahy... | 4312I-01920 | 1       |
| Euro OTC       | Sodium sulfate decahy... | 1108035-01  | 3       |
| Euro OTC       | Talcum                   | 1305022-02  | 1       |
| Euro OTC       | Talcum                   | 1210052-01  | 5       |
| Euro OTC       | Talcum                   | 1411014-01  | 1       |
| Euro OTC       | Talcum                   | 1305022-01  | 9       |
| Euro OTC       | Tocomax 20%              | 100912      | 1       |
| Euro OTC       | Tragacanth, powdered     | 12285401    | 1       |
| Euro OTC       | Tricalcium phosphate     | 1304025-01  | 2       |
| Euro OTC       | Tricalcium phosphate     | 1206002-01  | 4       |
| Euro OTC       | Zinc orotate dihydrate   | 1107029-1   | 1       |
| Euro OTC       | Zinc sulfate heptahyd... | 1309011_0   | 1       |
| Euro OTC       | Zinc sulfate heptahyd... | 1201031-2   | 1       |
| Euro OTC       | Zinc sulfate heptahyd... | 1201031-02  | 1       |
| Euro OTC       | Zinc sulfate heptahyd... | 1105002-01  | 2       |
| Euro OTC       | Zinc sulfate heptahyd... | 1201031-01  | 1       |
| EUro/AHD       | Calcium chloride dihy... | 1205014-02  | 2       |
| euroho/gehe    | Sodium hydrogen carbo... | 123030-02   | 1       |
| Euroo/Phoenix  | Aluminium chloride he... | 120014-02   | 1       |
| Extrakt Chemie | Cowberry extract 6:1     | 17320/01    | 1       |
| Fagron         | Methadone hydrochloride  | 1437H011    | 1       |
| Fagron         | 8-quinolinol sulfate ... | 10F01-N15   | 1       |
| Fagron         | 8-quinolinol sulfate ... | 11L08-N08   | 1       |
| Fagron         | 8-quinolinol sulfate ... | 13A04-N05   | 2       |
| Fagron         | 8-quinolinol sulfate ... | 13G10-N06   | 1       |

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| Supplier | Substance                | Batch            | Spectra |
|----------|--------------------------|------------------|---------|
| Fagron   | 8-quinolinol sulfate ... | 13032014C        | 1       |
| Fagron   | 8-quinolinol sulfate ... | 11I09-N09        | 1       |
| Fagron   | 8-quinolinol sulfate ... | 13D24-N11        | 1       |
| Fagron   | 8-quinolinol sulfate ... | 11L19-N14        | 1       |
| Fagron   | 8-quinolinol sulfate ... | 12A04-N05        | 1       |
| Fagron   | 8-quinolinol sulfate ... | 11L08-N07        | 2       |
| Fagron   | 8-quinolinol sulfate ... | 11/09-N09        | 1       |
| Fagron   | Alchemilla, cut          | 11182802         | 1       |
| Fagron   | Almonds, bitter, whole   | 40A121010        | 11      |
| Fagron   | Aluminium chloride he... | 11123-N06        | 3       |
| Fagron   | Aluminium chloride he... | 12/11-No3        | 1       |
| Fagron   | Aluminium chloride he... | 13d22no9         | 1       |
| Fagron   | Aluminium chloride he... | 11G05-N02        | 1       |
| Fagron   | Aluminium chloride he... | 11G05-No2        | 1       |
| Fagron   | Aluminium chloride he... | 12/27/N01        | 1       |
| Fagron   | Aluminium chloride he... | 12047512         | 4       |
| Fagron   | Aluminium chloride he... | 13D22.-N09       | 1       |
| Fagron   | Aluminium chloride he... | 12082013D        | 1       |
| Fagron   | Aluminium chloride he... | 13D22N09         | 2       |
| Fagron   | Aluminium chloride he... | 13D22-09         | 1       |
| Fagron   | Aluminium chloride he... | 12i27-N01        | 2       |
| Fagron   | Aluminium chloride he... | 1227N01          | 1       |
| Fagron   | Aluminium chloride he... |                  | 3       |
| Fagron   | Aluminium chloride he... | 12c07n01         | 1       |
| Fagron   | Aluminium chloride he... | 13126-N13        | 1       |
| Fagron   | Aluminium chloride he... | 12G05-N10        | 29      |
| Fagron   | Aluminium chloride he... | 12g05-n10        | 1       |
| Fagron   | Aluminium chloride he... | 12I-27-N01       | 1       |
| Fagron   | Aluminium chloride he... | 12127-N01        | 5       |
| Fagron   | Aluminium chloride he... | 12L11-N03        | 3       |
| Fagron   | Aluminium chloride he... | 1207211095       | 1       |
| Fagron   | Aluminium chloride he... | 11C07_N05        | 1       |
| Fagron   | Aluminium chloride he... | 1901211095       | 1       |
| Fagron   | Aluminium chloride he... | C181A            | 3       |
| Fagron   | Aluminium chloride he... | 13J31-B06-287615 | 1       |
| Fagron   | Aluminium chloride he... | 2405211095       | 1       |
| Fagron   | Aluminium chloride he... | 13I26-N13        | 2       |
| Fagron   | Aluminium chloride he... | 11/23-N06B206A   | 1       |
| Fagron   | Aluminium chloride he... | 12323702         | 17      |
| Fagron   | Aluminium chloride he... | 12G05-N0         | 1       |
| Fagron   | Aluminium chloride he... | 1910211095       | 1       |
| Fagron   | Aluminium chloride he... | 2013U-01095      | 1       |
| Fagron   | Aluminium chloride he... | 12I27-N01        | 12      |
| Fagron   | Aluminium chloride he... | 105282-0002      | 1       |
| Fagron   | Aluminium chloride he... | C145A            | 1       |
| Fagron   | Aluminium chloride he... | C012A            | 1       |
| Fagron   | Aluminium chloride he... | 8547287          | 1       |
| Fagron   | Aluminium chloride he... | 5213A1095        | 1       |
| Fagron   | Aluminium chloride he... | 11 23-N06        | 1       |
| Fagron   | Aluminium chloride he... | 2913U1095        | 1       |
| Fagron   | Aluminium chloride he... | 105282-0001      | 1       |
| Fagron   | Aluminium chloride he... | 20122013E        | 1       |
| Fagron   | Aluminium potassium s... | A1-063-AL        | 1       |
| Fagron   | Aluminium potassium s... | 13D08-N01        | 2       |
| Fagron   | Aluminium potassium s... | 103638           | 1       |
| Fagron   | Aluminium potassium s... | 11F20-M12        | 1       |
| Fagron   | Aluminium potassium s... | A1-063-A1        | 1       |
| Fagron   | Aluminium potassium s... | 13D29-N04        | 1       |
| Fagron   | Aluminium potassium s... | 12/24-M02        | 1       |
| Fagron   | Aluminium potassium s... | 12I24-M03        | 1       |

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| Supplier | Substance                | Batch            | Spectra |
|----------|--------------------------|------------------|---------|
| Fagron   | Amphetamine sulfate      | 13B11-N04        | 5       |
| Fagron   | Amphetamine sulfate      | 78012            | 1       |
| Fagron   | Amphetamine sulfate      | 324577           | 2       |
| Fagron   | Amphetamine sulfate      | 14E19-B09-294572 | 2       |
| Fagron   | Amphetamine sulfate      | 315291           | 1       |
| Fagron   | Amphetamine sulfate      | 11/01-N01        | 1       |
| Fagron   | Amphetamine sulfate      | 11D04-N13        | 1       |
| Fagron   | Amphetamine sulfate      | 13/18-B40-290538 | 1       |
| Fagron   | Amphetamine sulfate      | 2213Q-03361      | 1       |
| Fagron   | Amphetamine sulfate      | 96200            | 1       |
| Fagron   | Amphetamine sulfate      | 12/24N-03        | 1       |
| Fagron   | Amphetamine sulfate      | 12B06-N13        | 3       |
| Fagron   | Amphetamine sulfate      | 16A29-B03-318743 | 1       |
| Fagron   | Amphetamine sulfate      | 15101-b05-315292 | 1       |
| Fagron   | Amphetamine sulfate      | 13J18B40         | 1       |
| Fagron   | Amphetamine sulfate      | 13J18-B40-290538 | 2       |
| Fagron   | Amphetamine sulfate      | 12E11-N06        | 5       |
| Fagron   | Amphetamine sulfate      | 14E19-B09        | 2       |
| Fagron   | Amphetamine sulfate      | CH13B11-N04      | 1       |
| Fagron   | Amphetamine sulfate      | 16A29-B03        | 6       |
| Fagron   | Amphetamine sulfate      | 14E19-B09-304502 | 2       |
| Fagron   | Amphetamine sulfate      | 14E19-B09-294573 | 1       |
| Fagron   | Amphetamine sulfate      | 13J18-B40        | 1       |
| Fagron   | Amphetamine sulfate      | 88689            | 2       |
| Fagron   | Aniseed                  | 13037801         | 2       |
| Fagron   | Betaine hydrochloride    | 12C20-N09        | 1       |
| Fagron   | Betaine hydrochloride    | 24091301         | 1       |
| Fagron   | Betaine hydrochloride    | 15121401         | 1       |
| Fagron   | Betaine hydrochloride    | 13H13-N02        | 1       |
| Fagron   | Betaine hydrochloride    | 13G29-B02-294870 | 1       |
| Fagron   | Betamethasone-17-vale... | 13E08-N01        | 1       |
| Fagron   | Betamethasone-17-vale... | 12L19-N06        | 3       |
| Fagron   | Betamethasone-17-vale... | 12J19-N06        | 1       |
| Fagron   | Betamethasone-17-vale... | 12G02-N15        | 3       |
| Fagron   | Birch leaf, cut          | 7061301          | 1       |
| Fagron   | Bitter fennel            | 6858913          | 1       |
| Fagron   | Bitter fennel            | 12094708         | 3       |
| Fagron   | Bitter fennel            |                  | 1       |
| Fagron   | Bitter fennel            | 1406211545       | 1       |
| Fagron   | Black mustard seed, p... | 14293705         | 1       |
| Fagron   | Bogbean leaf, cut        | 2371B100616      | 1       |
| Fagron   | Caffeine citrate         | 2813E1282        | 1       |
| Fagron   | Caffeine citrate         | 4213U01282       | 1       |
| Fagron   | Caffeine citrate         | 11C29-N04        | 1       |
| Fagron   | Caffeine citrate         | 11/12-N13        | 1       |
| Fagron   | Caffeine citrate         | 10H02-N02        | 2       |
| Fagron   | Caffeine citrate         | 204311282        | 1       |
| Fagron   | Caffeine citrate         | CCD-1401         | 2       |
| Fagron   | Caffeine citrate         | CCC1205          | 1       |
| Fagron   | Caffeine citrate         | 3914U-01282      | 1       |
| Fagron   | Caffeine citrate         | 3314E-01282      | 1       |
| Fagron   | Caffeine citrate         | 2714E-01282      | 1       |
| Fagron   | Caffeine citrate         | 15a05-b03-318006 | 1       |
| Fagron   | Caffeine citrate         | 15A05-B03-318006 | 8       |
| Fagron   | Caffeine citrate         | 15A05-B03302747  | 1       |
| Fagron   | Caffeine citrate         | 15a05-b03-302746 | 1       |
| Fagron   | Caffeine citrate         | 15A05B03         | 1       |
| Fagron   | Caffeine citrate         | 15A05-B03        | 3       |
| Fagron   | Caffeine citrate         | 15A05-B03        | 1       |
| Fagron   | Caffeine citrate         | 13D30-N02        | 1       |

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| Supplier | Substance                | Batch            | Spectra |
|----------|--------------------------|------------------|---------|
| Fagron   | Caffeine citrate         | 13D30-N02        | 10      |
| Fagron   | Caffeine citrate         | 11C29-N04        | 1       |
| Fagron   | Caffeine citrate         | 11082015A        | 1       |
| Fagron   | Caffeine citrate         | 12J05-N06        | 1       |
| Fagron   | Caffeine citrate         | 2002311282       | 1       |
| Fagron   | Caffeine citrate         | 26021401         | 1       |
| Fagron   | Caffeine citrate         | 12C16-N03        | 2       |
| Fagron   | Caffeine citrate         | 3513I-01282      | 1       |
| Fagron   | Caffeine citrate         | 5013U01282       | 1       |
| Fagron   | Caffeine citrate         | 15A05-B03-307135 | 1       |
| Fagron   | Caffeine citrate         | 13D30-No2        | 1       |
| Fagron   | Calcium hydroxide        | 12G04-N22        | 1       |
| Fagron   | Calcium hydroxide        | 12J18-N01        | 1       |
| Fagron   | Calcium hydroxide        | 13D26-N14        | 1       |
| Fagron   | Calendula flower, cut    | 1241B120312      | 3       |
| Fagron   | Calendula flower, cut    | 1104211448       | 1       |
| Fagron   | Clobetasol-17-propion... | 12K08-N02        | 2       |
| Fagron   | Clobetasol-17-propion... | 12/19-N01003637  | 1       |
| Fagron   | Clobetasol-17-propion... | 12/19-No1        | 1       |
| Fagron   | Clobetasol-17-propion... | 12I19-N01        | 1       |
| Fagron   | Clobetasol-17-propion... | 12I19-N01        | 1       |
| Fagron   | Clobetasol-17-propion... | 13W16-N01        | 1       |
| Fagron   | Clobetasol-17-propion... | 12/19-N01        | 1       |
| Fagron   | Clobetasol-17-propion... | 12L19-N06        | 1       |
| Fagron   | Clobetasol-17-propion... | 12A03-N03        | 2       |
| Fagron   | Cocaine hydrochloride    | 12G23-N13        | 1       |
| Fagron   | Codeine phosphate hem... | 13/27-N06        | 2       |
| Fagron   | Codeine phosphate hem... | 913I-01279       | 1       |
| Fagron   | Codeine phosphate hem... | 13E21-N04        | 1       |
| Fagron   | Codeine phosphate hem... | 12C05-N01        | 1       |
| Fagron   | Codeine phosphate hem... | 11L20-N04        | 1       |
| Fagron   | Codeine phosphate hem... | 11/19-N10        | 1       |
| Fagron   | Codeine phosphate hem... | 16E17-B05-324109 | 2       |
| Fagron   | Codeine phosphate hem... | 1615I-01279      | 1       |
| Fagron   | Codeine phosphate hem... | 15F09-B02-310520 | 2       |
| Fagron   | Codeine phosphate hem... | 15B17-B99-304623 | 1       |
| Fagron   | Codeine phosphate hem... | 13C11-N10        | 1       |
| Fagron   | Codeine phosphate hem... | 13I27-N06        | 2       |
| Fagron   | Copper (II) sulfate p... | 13A25-N06        | 2       |
| Fagron   | Dexamethasone 1:10 (r... | 12C20-N03        | 4       |
| Fagron   | Dexamethasone 1:10 (r... | 12L19-N06        | 1       |
| Fagron   | Dexamethasone 1:10 (r... | 12K06-N09        | 1       |
| Fagron   | Dexamphetamine sulfate   | 13I23-N01        | 1       |
| Fagron   | Dexamphetamine sulfate   | 15H06-B04-313861 | 1       |
| Fagron   | Dexamphetamine sulfate   | 12J15-N07        | 1       |
| Fagron   | Dexamphetamine sulfate   | 11F29-N01        | 1       |
| Fagron   | Dihydrocodeine hydrog... | 13H19-N08        | 3       |
| Fagron   | Dihydrocodeine hydrog... | 14K26-B04-310974 | 1       |
| Fagron   | Dihydrocodeine hydrog... | 12G05-N01        | 1       |
| Fagron   | Dihydrocodeine hydrog... | 14D08-B06        | 1       |
| Fagron   | Dihydrocodeine hydrog... | 14K26-B04        | 1       |
| Fagron   | Dithranole               | 13A30-N01        | 4       |
| Fagron   | Dithranole               | 17710I-01274     | 1       |
| Fagron   | Dithranole               | APDT/375/2012D   | 15      |
| Fagron   | Dithranole               | Ch13A30-N01      | 1       |
| Fagron   | Fentanyl citrate         | 20100911-1       | 1       |
| Fagron   | Fentanyl citrate         | 12G02-N03        | 1       |
| Fagron   | Fentanyl citrate         | 10H20-N02        | 1       |
| Fagron   | Fenugreek, powdered      | 12149603         | 1       |
| Fagron   | Frankincense             |                  | 1       |

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| Supplier | Substance                | Batch            | Spectra |
|----------|--------------------------|------------------|---------|
| Fagron   | Fuchsine                 | 12G18-N01        | 1       |
| Fagron   | Fuchsine                 | 12A03-N06        | 2       |
| Fagron   | Fuchsine                 | 13A30-N05        | 2       |
| Fagron   | Fuchsine                 | 12F28-N02        | 1       |
| Fagron   | Fuchsine                 | 13H23-M04        | 2       |
| Fagron   | Heavy alkaline bismut... | 1001311186       | 1       |
| Fagron   | Heavy alkaline bismut... | 13B25-N02        | 4       |
| Fagron   | Heavy alkaline bismut... | 12D26-N03        | 1       |
| Fagron   | Heavy alkaline bismut... | 1309211186       | 1       |
| Fagron   | Heavy alkaline bismut... | 13C15-N05        | 3       |
| Fagron   | Heavy alkaline bismut... | 11/13-N01        | 1       |
| Fagron   | Heavy alkaline bismut... | 11D28-N16        | 1       |
| Fagron   | Heavy alkaline bismut... | 13H28-B04-291385 | 1       |
| Fagron   | Heavy alkaline bismut... | 42000079         | 1       |
| Fagron   | Heavy alkaline bismut... | 12d26-no3        | 1       |
| Fagron   | Heavy, basic magnesiu... | 13A10-N02        | 1       |
| Fagron   | Heavy, basic magnesiu... | 12F20-N04        | 1       |
| Fagron   | Hydromorphone hydroch... | 12G05-N02        | 1       |
| Fagron   | Indigo carmine           | 12A20-N067-16    | 1       |
| Fagron   | Indigo carmine           | 5093143          | 1       |
| Fagron   | Indigo carmine           | 13K12-N01        | 1       |
| Fagron   | Indigo carmine           | 5132316          | 1       |
| Fagron   | Indigo carmine           | 11F09-N06        | 1       |
| Fagron   | Indigo carmine           | 12K06-N11        | 1       |
| Fagron   | Ladys bedstraw herb,...  | 12369004         | 2       |
| Fagron   | Lungwort herb, cut       | Nachprüfung      | 1       |
| Fagron   | Macrogol 6000 powder,... | 14J17-B01        | 1       |
| Fagron   | Macrogol 6000 powder,... | 12J22-N02        | 1       |
| Fagron   | Macrogol 6000 powder,... | 11G14-N03        | 1       |
| Fagron   | Magnesium chloride he... | 1301c009-277802  | 1       |
| Fagron   | Magnesium chloride he... | 12H21-N02        | 1       |
| Fagron   | Magnesium chloride he... | 1301C009-277802  | 4       |
| Fagron   | Magnesium chloride he... | 12H21-No2        | 1       |
| Fagron   | Magnesium chloride he... | 1304C001-281211  | 2       |
| Fagron   | Magnesium chloride he... | 1301C011-277803  | 1       |
| Fagron   | Magnesium chloride he... | 1304C002         | 1       |
| Fagron   | Magnesium chloride he... | 1301C10-277801   | 2       |
| Fagron   | Magnesium chloride he... | 1301C012         | 1       |
| Fagron   | Magnesium chloride he... | 12h21-N02        | 1       |
| Fagron   | Magnesium chloride he... | M1625            | 2       |
| Fagron   | Magnesium chloride he... | M1430            | 1       |
| Fagron   | Magnesium chloride he... | 12H21-N02        | 13      |
| Fagron   | Magnesium chloride he... | 12D11-N01        | 1       |
| Fagron   | Magnesium chloride he... | 12D11-N01        | 5       |
| Fagron   | Magnesium chloride he... | 12B16-N01        | 7       |
| Fagron   | Magnesium chloride he... | 11K17-N10        | 3       |
| Fagron   | Magnesium chloride he... | 11K17-N01        | 1       |
| Fagron   | Magnesium chloride he... | 1301C012-277804  | 1       |
| Fagron   | Magnesium chloride he... | M1555            | 1       |
| Fagron   | Magnesium chloride he... | 1301C10          | 4       |
| Fagron   | Magnesium chloride he... | 26061305         | 1       |
| Fagron   | Magnesium chloride he... | 13B14-B01-287292 | 1       |
| Fagron   | Magnesium chloride he... | 13411207         | 1       |
| Fagron   | Magnesium chloride he... | 1304C004-281210  | 1       |
| Fagron   | Magnesium chloride he... | 1304c004-281210  | 1       |
| Fagron   | Magnesium chloride he... | 1304C003-281209  | 1       |
| Fagron   | Magnesium chloride he... | 1304C003         | 1       |
| Fagron   | Magnesium chloride he... | 29011304         | 1       |
| Fagron   | Magnesium sulfate hep... | 12L10-N07        | 1       |
| Fagron   | Magnesium sulfate hep... | 13H05-N02        | 1       |

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| Supplier | Substance                  | Batch            | Spectra |
|----------|----------------------------|------------------|---------|
| Fagron   | Magnesium sulfate hep. . . | 12G24-N02        | 1       |
| Fagron   | Magnesium sulfate hep. . . | 31161            | 2       |
| Fagron   | Marian thistle fruit       | 10270608         | 1       |
| Fagron   | Matricaria flower          |                  | 1       |
| Fagron   | Melissa leaf, cut          | 12032318         | 3       |
| Fagron   | Methadone hydrochloride    | 171920-0009      | 1       |
| Fagron   | Methadone hydrochloride    | 15E29-B02-309063 | 1       |
| Fagron   | Methadone hydrochloride    | 15E29_B02_309070 | 1       |
| Fagron   | Methadone hydrochloride    | 15B24-B02-304724 | 1       |
| Fagron   | Methadone hydrochloride    | 15B24-B02-304724 | 5       |
| Fagron   | Methadone hydrochloride    | 13J24B06286910   | 1       |
| Fagron   | Methadone hydrochloride    | 1514H042         | 2       |
| Fagron   | Methadone hydrochloride    | 14H15-B01-299386 | 1       |
| Fagron   | Methadone hydrochloride    | 14H15-B01-299382 | 4       |
| Fagron   | Methadone hydrochloride    | 14H15-B01-299380 | 1       |
| Fagron   | Methadone hydrochloride    | 14H15-B01        | 1       |
| Fagron   | Methadone hydrochloride    | 14C24-B01-292862 | 1       |
| Fagron   | Methadone hydrochloride    | 13B06-N02        | 6       |
| Fagron   | Methadone hydrochloride    | 12H07-N07        | 1       |
| Fagron   | Methadone hydrochloride    | 1437H012         | 3       |
| Fagron   | Methadone hydrochloride    | 1409H043         | 1       |
| Fagron   | Methadone hydrochloride    | 13J24-B06-286908 | 1       |
| Fagron   | Methadone hydrochloride    | 4031517          | 1       |
| Fagron   | Methadone hydrochloride    | 12b21-n03        | 1       |
| Fagron   | Methadone hydrochloride    | 8081501          | 1       |
| Fagron   | Methadone hydrochloride    | 1316H037         | 4       |
| Fagron   | Methadone hydrochloride    | 13F17-N02        | 4       |
| Fagron   | Methadone hydrochloride    | 12B21-N03        | 2       |
| Fagron   | Methadone hydrochloride    | 20130912-6       | 1       |
| Fagron   | Methadone hydrochloride    | 15E29-B02-309065 | 1       |
| Fagron   | Methadone hydrochloride    | 12H07-N05        | 4       |
| Fagron   | Methadone hydrochloride    | 14C24-B01-292857 | 4       |
| Fagron   | Methadone hydrochloride    | 9041306          | 1       |
| Fagron   | Methadone hydrochloride    | 414022-1-P       | 1       |
| Fagron   | Methadone hydrochloride    | 29051502         | 1       |
| Fagron   | Methadone hydrochloride    | 13J24-B06-286907 | 1       |
| Fagron   | Methadone hydrochloride    | 1225H008         | 1       |
| Fagron   | Methadone hydrochloride    | 25091406         | 1       |
| Fagron   | Methadone hydrochloride    | 17C24-B05-334309 | 1       |
| Fagron   | Methadone hydrochloride    | 16K01-B04-329937 | 1       |
| Fagron   | Methadone hydrochloride    | 16K01-B04        | 2       |
| Fagron   | Methadone hydrochloride    | 1213E-02949      | 1       |
| Fagron   | Methadone hydrochloride    | 16B16-B02-318421 | 1       |
| Fagron   | Methadone hydrochloride    | 1608H002         | 1       |
| Fagron   | Methadone hydrochloride    | 13J24-B06        | 1       |
| Fagron   | Methadone hydrochloride    | 1327h051         | 1       |
| Fagron   | Methadone hydrochloride    | 12A05-No2        | 1       |
| Fagron   | Methadone hydrochloride    | 11D07-N09        | 1       |
| Fagron   | Methadone hydrochloride    | 15B24-B02-313097 | 1       |
| Fagron   | Methadone hydrochloride    | 15I24-B07        | 1       |
| Fagron   | Methadone hydrochloride    | 14H15-B01-299381 | 1       |
| Fagron   | Methadone hydrochloride    | 25091307         | 1       |
| Fagron   | Methadone hydrochloride    | 15E29-B02-313098 | 3       |
| Fagron   | Methadone hydrochloride    | 15E29-B02-309070 | 2       |
| Fagron   | Methadone hydrochloride    | 16B16-B02-318420 | 1       |
| Fagron   | Methadone hydrochloride    | 11G11-N02        | 1       |
| Fagron   | Methadone hydrochloride    | 13I24-B06-286908 | 1       |
| Fagron   | Methylrosanilinium ch. . . | 13184811         | 1       |
| Fagron   | Methylrosanilinium ch. . . | 12D19-0005       | 1       |
| Fagron   | Methylrosanilinium ch. . . | 13H28-N03        | 2       |

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| Supplier | Substance                | Batch               | Spectra |
|----------|--------------------------|---------------------|---------|
| Fagron   | Methylrosanilinium ch... | 13G03-N11           | 2       |
| Fagron   | Methylrosanilinium ch... | 12I17-N05           | 2       |
| Fagron   | Methylrosanilinium ch... | 13H28-N03-0161-1030 | 1       |
| Fagron   | Methylrosanilinium ch... | 13H28-N03           | 2       |
| Fagron   | Methylrosanilinium ch... | 13G03-N011          | 1       |
| Fagron   | Methylrosanilinium ch... | 12D19-N01           | 4       |
| Fagron   | Methylrosanilinium ch... | 12-17-N050109-140   | 1       |
| Fagron   | Methylrosanilinium ch... | 12H28-N06           | 1       |
| Fagron   | Methylrosanilinium ch... | 13G03N11            | 1       |
| Fagron   | Midazolam                | 14C12-B31-313222    | 1       |
| Fagron   | Midazolam                | 16J03-B09-326963    | 1       |
| Fagron   | Midazolam hydrochloride  | 14C19-B04           | 1       |
| Fagron   | Midazolam hydrochloride  | 14H05-B08-297982    | 1       |
| Fagron   | Midazolam hydrochloride  | 9D27-N01            | 2       |
| Fagron   | Midazolam hydrochloride  | 13E22-N09           | 2       |
| Fagron   | Morphine hydrochloride   | 13H22-N12           | 1       |
| Fagron   | Morphine hydrochloride   | 15I09-B08-312693    | 1       |
| Fagron   | Morphine hydrochloride   | 13D09-N04           | 1       |
| Fagron   | Morphine hydrochloride   | 12E10-N04           | 2       |
| Fagron   | Morphine hydrochloride   | 12E10N04            | 1       |
| Fagron   | Morphine hydrochloride   | B03-292079          | 1       |
| Fagron   | Morphine hydrochloride   | 11A27-N04           | 1       |
| Fagron   | Morphine hydrochloride   | 15J27_B01_316889    | 1       |
| Fagron   | Morphine hydrochloride   | 15A12-B04-303137    | 1       |
| Fagron   | Naloxone hydrochloride   | 13L12-B03-289511    | 1       |
| Fagron   | Naloxone hydrochloride   | 13H09-N08           | 1       |
| Fagron   | Naloxone hydrochloride   | 13D22-N07           | 3       |
| Fagron   | Naloxone hydrochloride   | 12G19-N02           | 1       |
| Fagron   | Naloxone hydrochloride   | 12G19-N02           | 2       |
| Fagron   | Naloxone hydrochloride   | 11/23-N01           | 1       |
| Fagron   | Naloxone hydrochloride   | 12-00071            | 2       |
| Fagron   | Nettle leaf, cut         | 12184702            | 4       |
| Fagron   | Nystatin                 | 11C21-N10           | 1       |
| Fagron   | Nystatin                 | 4014376             | 1       |
| Fagron   | Nystatin                 | 11L21-N02           | 1       |
| Fagron   | Nystatin                 | 12C29-N09           | 3       |
| Fagron   | Nystatin                 | 12G04-N12           | 1       |
| Fagron   | Nystatin                 | 13C11-N08           | 1       |
| Fagron   | Nystatin                 | 20121202            | 1       |
| Fagron   | Nystatin                 | 11K11-No4           | 1       |
| Fagron   | Nystatin                 | 11K11-N04           | 1       |
| Fagron   | Orris root               | 11026705            | 3       |
| Fagron   | Peppermint leaf, cut     | 1234567             | 2       |
| Fagron   | Peppermint leaf, cut     | 13030803            | 3       |
| Fagron   | Phenobarbital            | 15G07-B06-311718    | 1       |
| Fagron   | Phenobarbital            | 13G05-N09           | 2       |
| Fagron   | Potassium hydrocarbon... | 120801001           | 1       |
| Fagron   | Potassium hydrocarbon... | 3413M-01728         | 1       |
| Fagron   | Potassium hydrocarbon... | 10G22-N10           | 1       |
| Fagron   | Potassium hydrocarbon... | 11/26-N14           | 1       |
| Fagron   | Potassium hydrocarbon... | 13031205            | 1       |
| Fagron   | Potassium hydrocarbon... | 12K27-N06           | 2       |
| Fagron   | Potassium hydrocarbon... | 12C12-N02           | 2       |
| Fagron   | Potassium hydrocarbon... | 12141911            | 1       |
| Fagron   | Prednisolone 1:10 (ri... | 12D04-N01           | 1       |
| Fagron   | Prednisolone 1:10 (ri... | 12L19-N06           | 1       |
| Fagron   | Psyllium seed            | 3610U-02243         | 1       |
| Fagron   | Rhubarb, powdered        | 11043821            | 1       |
| Fagron   | Rutoside trihydrate      | L14050127           | 1       |
| Fagron   | Rutoside trihydrate      | 13K12-B06           | 1       |

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| Supplier | Substance                | Batch             | Spectra |
|----------|--------------------------|-------------------|---------|
| Fagron   | Sage leaf, cut           | 2301A120403       | 49      |
| Fagron   | Senna leaf, cut          | 314Q1514          | 1       |
| Fagron   | Sodium alginate          | 14G22-B99         | 1       |
| Fagron   | Sodium carbonate deca... | 12B16-N01         | 1       |
| Fagron   | Sodium dihydrogen pho... | 12L05-N05         | 1       |
| Fagron   | Sodium hydrogen carbo... | 13B12-N01         | 1       |
| Fagron   | Sodium hydrogen carbo... | 13B18-N03         | 6       |
| Fagron   | Sodium hydrogen carbo... | RBA3421100        | 6       |
| Fagron   | Sodium hydrogen carbo... | 11e31-n04         | 1       |
| Fagron   | Sodium hydrogen carbo... | 11K25-N05         | 4       |
| Fagron   | Sodium hydrogen carbo... | 12B06-N01         | 3       |
| Fagron   | Sodium hydrogen carbo... | 13D29-N09         | 6       |
| Fagron   | Sodium hydrogen carbo... | 12D11N02          | 2       |
| Fagron   | Sodium hydrogen carbo... | RBA3631200        | 1       |
| Fagron   | Sodium hydrogen carbo... | 12D11-N02         | 2       |
| Fagron   | Sodium hydrogen carbo... | RBA0021100        | 1       |
| Fagron   | Sodium hydrogen carbo... | RBA3651200        | 2       |
| Fagron   | Sodium hydrogen carbo... | 4413I01892        | 1       |
| Fagron   | Sodium hydrogen carbo... | 13G11-N03         | 3       |
| Fagron   | Sodium hydrogen carbo... | 11/12-N16         | 2       |
| Fagron   | Sodium hydrogen carbo... | RBA1661100        | 1       |
| Fagron   | Sodium hydrogen carbo... | 11I12-N16         | 5       |
| Fagron   | Sodium hydrogen carbo... | 12D11-No2         | 1       |
| Fagron   | Sodium hydrogen carbo... | 12G11-N03         | 9       |
| Fagron   | Sodium hydroxide pell... | 13k22-no5         | 1       |
| Fagron   | Sodium hydroxide pell... | 13F06-N02         | 3       |
| Fagron   | Sodium hydroxide pell... | 12E02-N15         | 2       |
| Fagron   | Sodium monohydrogenph... | 13D24-N12         | 3       |
| Fagron   | Sodium monohydrogenph... | 12H21-N03         | 1       |
| Fagron   | Sodium monohydrogenph... | 13H01-B01         | 1       |
| Fagron   | Sodium monohydrogenph... | 613I-01914        | 1       |
| Fagron   | Sodium monohydrogenph... | 11K07-N10         | 1       |
| Fagron   | Sodium monohydrogenph... | B44888A           | 2       |
| Fagron   | Sodium monohydrogenph... | 2111E-01914       | 1       |
| Fagron   | Sodium monohydrogenph... | 1513I-01914       | 1       |
| Fagron   | Sodium monohydrogenph... | 11K30-N01         | 1       |
| Fagron   | Sodium sulfate decahy... | 11H01-N06         | 1       |
| Fagron   | Sodium sulfate decahy... | 12E30-N09         | 1       |
| Fagron   | Sodium sulfate decahy... | 12H31-N04         | 2       |
| Fagron   | Sodium sulfate decahy... | 1464              | 1       |
| Fagron   | Sodium sulfate decahy... | 2134              | 2       |
| Fagron   | Sodium thiosulfate pe... | 13092013E         | 1       |
| Fagron   | Sodium thiosulfate pe... | 12F20-N10         | 1       |
| Fagron   | Sodium thiosulfate pe... | 12F20-N20         | 1       |
| Fagron   | Sodium thiosulfate pe... | 3313U-01922       | 1       |
| Fagron   | Sodium thiosulfate pe... | 14A28-B08-290696  | 1       |
| Fagron   | Sulfanilamide            | 11L01-No8         | 1       |
| Fagron   | Thiomersal               | 12C08-N02         | 1       |
| Fagron   | Thiomersal               | 12F19-N11         | 1       |
| Fagron   | Thiomersal               | 12J17-N02         | 1       |
| Fagron   | Thiomersal               | 13E22-N13         | 1       |
| Fagron   | Triamcinolone acetoni... | 12I07-N04         | 1       |
| Fagron   | Triamcinolone acetoni... | 14F17-N02         | 1       |
| Fagron   | Triamcinolone acetoni... | 13F21-N01         | 2       |
| Fagron   | Triamcinolone acetoni... | 13F20-N010113/150 | 1       |
| Fagron   | Triamcinolone acetoni... | 12I07-N04         | 1       |
| Fagron   | Triamcinolone acetoni... | 11G14-N02         | 1       |
| Fagron   | Triamcinolone acetoni... | 12I07-N04022/359  | 1       |
| Fagron   | Triamcinolone acetoni... | 12F21-N01         | 1       |
| Fagron   | Triamcinolone acetoni... | 12I07-No4         | 1       |

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| Supplier                 | Substance                | Batch             | Spectra |
|--------------------------|--------------------------|-------------------|---------|
| Fagron                   | Triamcinolone acetoni... | 12G23-N06         | 3       |
| Fagron                   | Triamcinolone acetoni... | 12E23-N01         | 5       |
| Fagron                   | Tricalcium phosphate     | 12I13-N03         | 1       |
| Fagron                   | Tricalcium phosphate     | 12G10-N05         | 1       |
| Fagron                   | Trichloroacetic acid     | 13H22-M04         | 1       |
| Fagron                   | Trichloroacetic acid     | 10379405          | 1       |
| Fagron                   | Trichloroacetic acid     | 13B19-M04         | 1       |
| Fagron                   | Wild pansy, cut          |                   | 1       |
| Fagron                   | Yarrow herb, cut         | 3613M-0165        | 1       |
| Falcento                 | D-(+)-mannose            | R-4638            | 1       |
| Falcento                 | D-(+)-mannose            | R-4639            | 2       |
| Falcento                 | D-(+)-mannose            | R-4641            | 1       |
| Falcento                 | D-(+)-mannose            | R4640             | 1       |
| Falcento                 | D-ribose                 | 201206712         | 2       |
| Falcento                 | D-ribose                 | JXCZSJ14-D-010    | 1       |
| Falcento                 | D-ribose                 | 201209702         | 1       |
| fargon                   | Magnesium sulfate hep... | 12E22-N02         | 4       |
| Fargon                   | Caffeine citrate         | 12J05-N06         | 4       |
| Fargon                   | Caffeine citrate         | 11F21-N05         | 1       |
| Fargon                   | Heavy alkaline bismut... | 11C10-N06         | 1       |
| Fargon                   | Hydromorphone hydroch... | 13I27-N05         | 1       |
| FARGON                   | Aluminium chloride he... | 13d22-n09         | 1       |
| Fargon/17.07.2013/Now... | Triamcinolone acetoni... | 12I07-N04         | 1       |
| Fargon/Phoenix           | Caffeine citrate         | 15A05-B03-302746  | 11      |
| Fargron                  | Triamcinolone acetoni... | 11E19-N011        | 1       |
| Fargron/Noweda           | Sweet fennel             | 2870A150810       | 1       |
| Faron                    | Aluminium chloride he... | 13I13-B03-287298  | 1       |
| Fgron                    | Caffeine citrate         | 2013Q-01282       | 1       |
| Fiebig                   | Acorus root, peeled      | 6701B120427       | 9       |
| Fiebig                   | Aluminium chloride he... | 11J06-N03         | 1       |
| Fiebig                   | Dandelion herb with r... | 11003313          | 1       |
| Fiebig                   | Frankincense             | 10349213          | 3       |
| Fiebig                   | Ginkgo leaf, cut         | 13340902          | 1       |
| Fiebig                   | Ginkgo leaf, cut         | 12373604          | 4       |
| Fiebig                   | Mistletoe, cut           | 10273406          | 1       |
| Fiebig                   | White deadnettle herb... | 11371710          | 3       |
| Fiebig 04.01.13 ek: 1... | Bilberry fruit, dried    | 2910N110304       | 6       |
| Fiebig 05.11.12 ek:9...  | Bilberry fruit, dried    | 2910A120410       | 2       |
| Fiebig 14.02.13 ek:3...  | Melilot herb, cut        | 12231701          | 3       |
| Finze                    | Centaury, cut            | 11097610          | 3       |
| Finze                    | Elder flower, rubbed     | 9297415           | 3       |
| Finze                    | Equisetum stem, cut      | 11076305          | 10      |
| Finze                    | Knotgrass, cut           | 10237202          | 1       |
| Finze                    | Linseed                  | 3607E-02240       | 1       |
| Finze                    | Lycopodium herb, cut     | 9378803           | 1       |
| Finze                    | Male speedwell wort, ... | 4661B080915       | 1       |
| Finze                    | Male speedwell wort, ... | 4661B110121       | 2       |
| Finze                    | Matricaria flower        | 1290B101122       | 1       |
| Finze                    | Matricaria flower        | 12361703          | 8       |
| Finze                    | Sodium hydrogen carbo... | Pr.Nr.4311Q-01892 | 1       |
| Finze                    | St. John's wort, cut     | 9297303           | 1       |
| Finze                    | Wild thyme, cut          | 11031204          | 1       |
| fischar                  | Sodium hydrogen carbo... | 6522101           | 6       |
| Fischar                  | Copper (II) sulfate p... | 9452011           | 1       |
| Fischar                  | Sodium hydrogen carbo... | 6521111           | 9       |
| fragon                   | Sodium sulfate decahy... |                   | 1       |
| Gahlke                   | Aniseed, pounded         | 21401             | 1       |
| Gahlke                   | Bitter fennel            | 20362             | 1       |
| Gahlke                   | Frankincense             | 21949             | 1       |
| Gahlke                   | Parsley root, cut        | 20872             | 1       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b> | <b>Spectra</b> |
|-----------------|--------------------------|--------------|----------------|
| Gahlke          | Sorrel herb, cut         | 21479        | 1              |
| Gahlke          | Sweet woodruff herb, ... | 22100        | 1              |
| galke           | Aniseed                  | 19654        | 1              |
| galke           | Bitter fennel            | 19938        | 3              |
| galke           | Matricaria flower        | 18471        | 6              |
| galke           | Melissa leaf, cut        | 20867        | 1              |
| galke           | Nettle leaf, cut         | 21639        | 1              |
| galke           | Yellow chaste weed, cut  | nachprüfung  | 1              |
| Galke           | Acorus root, peeled      | 18944        | 1              |
| Galke           | Agrimony, cut            | 2002         | 1              |
| Galke           | Alchemilla, cut          | 21141        | 1              |
| Galke           | Alchemilla, cut          | 19835        | 1              |
| Galke           | Alchemilla, cut          | 22291        | 1              |
| Galke           | Aniseed                  | 22274        | 1              |
| Galke           | Aniseed                  | 21278        | 1              |
| Galke           | Aniseed                  | 23464        | 1              |
| Galke           | Asparagus root, cut      | 20178        | 1              |
| Galke           | Bean shells, cut         | 21219        | 1              |
| Galke           | Bearberry leaf, cut      | 19936        | 3              |
| Galke           | Birch leaf, cut          | 20904        | 1              |
| Galke           | Birch leaf, cut          | 21226        | 1              |
| Galke           | Bitter fennel            | 22176        | 1              |
| Galke           | Blackcurrants            | 21348        | 1              |
| Galke           | Blue bottle flower wi... | 23131        | 2              |
| Galke           | Boldo leaf, cut          | 19855        | 1              |
| Galke           | Burdock root, cut        | 19802        | 1              |
| Galke           | Caraway fruit            | 21257        | 1              |
| Galke           | Caraway fruit            | 27450        | 1              |
| Galke           | Caraway fruit            | 23627        | 1              |
| Galke           | Caraway fruit, pounded   | 18943        | 1              |
| Galke           | Centaury, cut            | 9721         | 1              |
| Galke           | Chelidonium majus her... | 20937        | 3              |
| Galke           | Common broom herb, cut   | 12358803     | 4              |
| Galke           | Common broom herb, cut   | 21610        | 1              |
| Galke           | Common wormwood herb,... | 21637        | 1              |
| Galke           | Couch grass rhizome, ... | 18781        | 1              |
| Galke           | Dandelion herb with r... | 22093        | 2              |
| Galke           | Dandelion herb with r... | 20531        | 6              |
| Galke           | Dandelion root, cut      | 126302       | 1              |
| Galke           | Dandelion root, cut      | 20658        | 1              |
| Galke           | Devil's claw root        | 21018        | 2              |
| Galke           | Devil's claw root        | 20282        | 2              |
| Galke           | Dill fruit               | 22422        | 4              |
| Galke           | Elder flower, rubbed     | 21934        | 1              |
| Galke           | Elecampane rhizome, cut  | 21569        | 2              |
| Galke           | Equisetum stem, cut      | 19663        | 5              |
| Galke           | Equisetum stem, cut      | 22061        | 1              |
| Galke           | Euphrasy herb, cut       | 20262        | 2              |
| Galke           | Gentian root, cut        | 19192        | 2              |
| Galke           | Geum urbanum herb, cut   | 20881        | 1              |
| Galke           | Ginger, peeled           | 20633        | 1              |
| Galke           | Ginger, peeled           | 21766        | 2              |
| Galke           | Goat's rue, cut          | 8378         | 2              |
| Galke           | Hawthorn leaf with fl... | 21126        | 3              |
| Galke           | Hay flower               | 21926        | 1              |
| Galke           | Hop strobile             | 20928        | 2              |
| Galke           | Hop strobile             | 20928        | 3              |
| Galke           | Hop strobile             | 23363        | 1              |
| Galke           | Horse chestnut flower... | 2614         | 1              |
| Galke           | Hyssop herb, cut         | 20939        | 1              |

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| Supplier | Substance                | Batch | Spectra |
|----------|--------------------------|-------|---------|
| Galke    | Iceland moss, cut        | 12369 | 1       |
| Galke    | Ladys bedstraw herb,...  | 21942 | 2       |
| Galke    | Lavender flower          | 21416 | 2       |
| Galke    | Lemon peel, cut          | 22975 | 1       |
| Galke    | Liquorice root, peeled   | 23538 | 1       |
| Galke    | Lungwort herb, cut       | 19511 | 4       |
| Galke    | Lycopodium herb, cut     | 16913 | 3       |
| Galke    | Mallow flower, cut       | 21119 | 1       |
| Galke    | Mallow leaf, cut         | 17133 | 1       |
| Galke    | Mallow leaf, cut         | 21445 | 1       |
| Galke    | Mallow leaf, cut         | 21454 | 1       |
| Galke    | Manna, powdered          | 20669 | 1       |
| Galke    | Manna, powdered          | 19784 | 1       |
| Galke    | Marian thistle fruit     | 22187 | 4       |
| Galke    | Marjoram herb, rubbed    | 22401 | 1       |
| Galke    | Marjoram herb, rubbed    | 23241 | 1       |
| Galke    | Masterwort root, cut     | 18411 | 1       |
| Galke    | Masterwort root, cut     | 23074 | 1       |
| Galke    | Maté leaf, cut           | 22365 | 1       |
| Galke    | Matricaria flower        | 21652 | 1       |
| Galke    | Matricaria flower        | 18803 | 1       |
| Galke    | Meadowsweet herb, cut    | 20358 | 1       |
| Galke    | Mistletoe, cut           | 20328 | 1       |
| Galke    | Mistletoe, cut           | 22012 | 2       |
| Galke    | Nettle leaf, cut         | 23302 | 1       |
| Galke    | Nettle leaf, cut         | 21238 | 1       |
| Galke    | Nettle leaf, cut         | 20956 | 1       |
| Galke    | Nutmeg, powdered (spi... | 22739 | 1       |
| Galke    | Oak bark, cut            | 17824 | 2       |
| Galke    | Orris root               | 21303 | 1       |
| Galke    | Peppermint leaf, cut     | 22218 | 1       |
| Galke    | Peppermint leaf, cut     | 22783 | 3       |
| Galke    | Peppermint leaf, cut     | 20975 | 3       |
| Galke    | Primrose flower          | 22612 | 2       |
| Galke    | Psyllium seed            | 20968 | 2       |
| Galke    | Psyllium seed            | 22989 | 7       |
| Galke    | Raspberry leaf, cut      | 19499 | 2       |
| Galke    | Raspberry leaf, cut      | 18060 | 2       |
| Galke    | Raspberry leaf, cut      | 23532 | 1       |
| Galke    | Raspberry leaf, cut      | 21244 | 1       |
| Galke    | Red clover flower        | 23128 | 2       |
| Galke    | Red-rose petal           | 22641 | 2       |
| Galke    | Restharrow root, cut     | 12700 | 1       |
| Galke    | Ribwort plantain, cut    | 21598 | 1       |
| Galke    | Ribwort plantain, cut    | 20259 | 1       |
| Galke    | Rosemary leaf, cut       | 21390 | 1       |
| Galke    | Rosemary leaf, cut       | 22777 | 1       |
| Galke    | Rosemary leaf, cut       | 19813 | 1       |
| Galke    | Sage leaf, cut           | 21015 | 3       |
| Galke    | Sanicle herb, cut        | 23097 | 1       |
| Galke    | Senna leaf, cut          | 21778 | 1       |
| Galke    | Shepherd's purse, cut    | 19483 | 1       |
| Galke    | Shepherd's purse, cut    | 21719 | 2       |
| Galke    | Silverweed, cut          | 12891 | 2       |
| Galke    | St. John's wort, cut     | 21990 | 4       |
| Galke    | St. John's wort, cut     | 21034 | 1       |
| Galke    | St. John's wort, cut     | 21556 | 1       |
| Galke    | St. John's wort, cut     | 23054 | 1       |
| Galke    | Tall golden rod, cut     | 21079 | 2       |
| Galke    | Thyme, rubbed            | 28719 | 1       |

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| Supplier          | Substance                | Batch         | Spectra |
|-------------------|--------------------------|---------------|---------|
| Galke             | Thyme, rubbed            | 19386         | 2       |
| Galke             | Thyme, rubbed            | 1833          | 1       |
| Galke             | Thyme, rubbed            | 20719         | 2       |
| Galke             | Tormentil                | 21091         | 1       |
| Galke             | Tormentil                | 21744         | 2       |
| Galke             | Turmeric root, cut       | 23123         | 1       |
| Galke             | Turmeric root, cut       | 20184         | 1       |
| Galke             | Turmeric, javanese, cut  | 15540         | 1       |
| Galke             | Turmeric, javanese, cut  | 15540         | 1       |
| Galke             | Valerian root, cut       | 21798         | 4       |
| Galke             | Valerian root, cut       | 22070         | 1       |
| Galke             | Walnut leaf, cut         | 21061         | 1       |
| Galke             | White deadnettle flower  | 21691         | 4       |
| Galke             | White deadnettle flower  | 22704         | 1       |
| Galke             | White deadnettle herb... | 22253         | 2       |
| Galke             | White deadnettle herb... | 19706         | 1       |
| Galke             | Willow bark, cut         | 20338         | 1       |
| Galke             | Willowherb, small flo... | 47502         | 1       |
| Galke             | Willowherb, small flo... | 22347         | 4       |
| Galke             | Wormwood herb, cut       | 21330         | 1       |
| Galke             | Yarrow herb, cut         | 23318         | 1       |
| Galke             | Yarrow herb, cut         | 23735         | 1       |
| Galke             | Yarrow herb, cut         | 21295         | 2       |
| Galke             | Yarrow herb, cut         | 22048         | 7       |
| galke,            | Calendula flower         | 12028         | 1       |
| galke,            | Lime flower, cut         | 2098          | 1       |
| gasser            | Angelica root            | 950049        | 1       |
| Gatt Koller/Herba | Amphetamine sulfate      | 942/03130814  | 1       |
| Gatt-Koller       | Betaine hydrochloride    | 2970/07102910 | 1       |
| gebepharm         | Sodium monohydrogenph... | 20160909-2    | 1       |
| gehe              | Agnus castus fruit       | 13193407      | 1       |
| gehe              | Cinnamon, cut            | 13304412      | 1       |
| Gehe              | Acorus root, peeled      | 6701B130807   | 12      |
| Gehe              | Alchemilla, cut          | 1341102       | 1       |
| Gehe              | Aluminium chloride he... | 1204026-01    | 28      |
| Gehe              | Aluminium chloride he... | 12/27-No1     | 1       |
| Gehe              | Aluminium chloride he... | 130701102     | 1       |
| Gehe              | Aluminium chloride he... | 12/27-n01     | 2       |
| Gehe              | Aluminium chloride he... | 12114902      | 5       |
| Gehe              | Angelica root            | 285732        | 1       |
| Gehe              | Angelica root            | 269740        | 2       |
| Gehe              | Aniseed, pounded         | 13149903      | 1       |
| Gehe              | Arnica flower            | 11259801      | 2       |
| Gehe              | Barberries               | 2720N111109   | 1       |
| Gehe              | Betamethasone-17-vale... | 12C19-N07     | 3       |
| Gehe              | Betamethasone-17-vale... | 12G02-N02     | 4       |
| Gehe              | Betony herb, cut         | 12007201      | 2       |
| Gehe              | Birch leaf, cut          | 264603        | 2       |
| Gehe              | Bitter fennel            | 12035102      | 3       |
| Gehe              | Blackberry leaf, cut     | 10136409      | 2       |
| Gehe              | Caffeine citrate         | 13B08-N02     | 3       |
| Gehe              | Calcium hydroxide        | 12F08-N02     | 3       |
| Gehe              | Calendula flower, cut    | 266676        | 1       |
| Gehe              | Calendula flower, cut    | 260205        | 1       |
| Gehe              | Chickweed, cut           | 10359112      | 1       |
| Gehe              | Chicory herb, cut        | 10325608      | 1       |
| Gehe              | Clobetasol-17-propion... | 1109D005      | 1       |
| Gehe              | Clobetasol-17-propion... | 12/19-N01     | 2       |
| Gehe              | Codeine phosphate hem... | 15350710      | 2       |
| Gehe              | Coltsfoot leaf, cut      | 269261        | 2       |

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| Supplier | Substance                | Batch        | Spectra |
|----------|--------------------------|--------------|---------|
| Gehe     | Couch grass rhizome, ... | 283061       | 1       |
| Gehe     | Couch grass rhizome, ... | 12186704     | 1       |
| Gehe     | Dandelion herb with r... | 6611B120620  | 29      |
| Gehe     | Dandelion herb with r... | 13019803     | 1       |
| Gehe     | Dandelion herb with r... | 266855       | 1       |
| Gehe     | Dandelion herb with r... | 6611B110104  | 1       |
| Gehe     | Dandelion herb withou... | 4591C111010  | 2       |
| Gehe     | Devil's claw root        | 1114005      | 1       |
| Gehe     | Dexamethasone 1:10 (r... | 12E30-N16    | 1       |
| Gehe     | Dill fruit               | 2680A121211  | 4       |
| Gehe     | Elder berries            | 12267807     | 1       |
| Gehe     | Elecampane rhizome, cut  | 12113302     | 2       |
| Gehe     | Elecampane rhizome, cut  | 11196906     | 1       |
| Gehe     | Elecampane rhizome, cut  | 1116905      | 1       |
| Gehe     | Equisetum stem, cut      | 10375510     | 2       |
| Gehe     | Equisetum stem, cut      | 10375515     | 1       |
| Gehe     | Fenugreek                | 13013811     | 2       |
| Gehe     | Frangula bark, cut       | 11254004     | 7       |
| Gehe     | Frangula bark, cut       | 11254003     | 2       |
| Gehe     | Frangula bark, cut       | 11254006     | 6       |
| Gehe     | Frankincense             | 12120002     | 1       |
| Gehe     | Fumitory, cut            | 13202907     | 1       |
| Gehe     | Galeopsis herb, cut      | 3911A130320  | 6       |
| Gehe     | Hawthorn leaf with fl... | 1351B111207  | 2       |
| Gehe     | Horse chestnut leaf, ... | 2551B131024  | 1       |
| Gehe     | Iceland moss, cut        | 11053915     | 1       |
| Gehe     | Iceland moss, cut        | 5191A130116  | 2       |
| Gehe     | Iceland moss, cut        | 11101605     | 2       |
| Gehe     | Iceland moss, cut        | 13350805     | 7       |
| Gehe     | Iceland moss, cut        | 11101603     | 2       |
| Gehe     | Ivy leaf, cut            | 11229501     | 1       |
| Gehe     | Liquorice root, peeled   | 268835       | 2       |
| Gehe     | Liquorice root, natur... | 283316       | 1       |
| Gehe     | Liquorice root, natur... | 277004       | 2       |
| Gehe     | Lycopodium herb, cut     | 521103845    | 1       |
| Gehe     | Mallow leaf, cut         | 10290512     | 2       |
| Gehe     | Marjoram herb, rubbed    | 4881A100929  | 4       |
| Gehe     | Matricaria flower        | 270579       | 1       |
| Gehe     | Matricaria flower        | 268408       | 2       |
| Gehe     | Matricaria flower        | 265419       | 4       |
| Gehe     | Matricaria flower        | 281103       | 5       |
| Gehe     | Matricaria flower        | 11255204     | 1       |
| Gehe     | Matricaria flower        | 276095       | 12      |
| Gehe     | Matricaria flower        | 12337605     | 1       |
| Gehe     | Matricaria flower        | 12133009     | 1       |
| Gehe     | Melilot herb, cut        | 110324       | 1       |
| Gehe     | Mistletoe, cut           | 264539       | 1       |
| Gehe     | Nettle leaf, cut         | 10162701     | 1       |
| Gehe     | Nettle root, cut         | 6631B120927  | 15      |
| Gehe     | Parsley herb, rubbed     | 10269905     | 1       |
| Gehe     | Parsley root, cut        | 6441A110210  | 4       |
| Gehe     | Peppermint leaf, cut     | 2161A121029  | 17      |
| Gehe     | Peppermint leaf, cut     | 2181B130717A | 1       |
| Gehe     | Peppermint leaf, cut     | 2181B130717B | 1       |
| Gehe     | Primrose flower          | 11374401     | 1       |
| Gehe     | Rhubarb, cut             | 11057817     | 6       |
| Gehe     | Rhubarb, cut             | 13235208     | 2       |
| Gehe     | Ribwort plantain, cut    | 4271A111125  | 3       |
| Gehe     | Rose hips with peel, ... | 2840A120719  | 1       |
| Gehe     | Rue herb, cut            | 12148802     | 1       |

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| Supplier                | Substance                | Batch        | Spectra |
|-------------------------|--------------------------|--------------|---------|
| Gehe                    | Sage leaf, cut           | 277580       | 7       |
| Gehe                    | Sage leaf, cut           | 265630       | 4       |
| Gehe                    | Sage leaf, cut           | 275598       | 5       |
| Gehe                    | Sage leaf, cut           | 269030       | 6       |
| Gehe                    | Shepherd's purse, cut    | 11036410     | 2       |
| Gehe                    | Silverweed, cut          | 11328101     | 1       |
| Gehe                    | Sodium hydrogen carbo... | 11078315     | 1       |
| Gehe                    | Sodium monohydrogenph... | 12109001     | 2       |
| Gehe                    | St. John's wort, cut     | 9297305      | 1       |
| Gehe                    | St. John's wort, cut     | 259604       | 1       |
| Gehe                    | St. John's wort, cut     | 11185602     | 1       |
| Gehe                    | Tall golden rod, cut     | 11207011     | 2       |
| Gehe                    | Thyme, rubbed            | 4622A110120  | 1       |
| Gehe                    | Triamcinolone acetoni... | 12A05-N07    | 4       |
| Gehe                    | Triamcinolone acetoni... | 13A15-N05    | 2       |
| Gehe                    | Walnut bark, cut         | 1135602      | 1       |
| Gehe                    | Walnut leaf, cut         | 10050412     | 1       |
| Gehe                    | Walnut leaf, cut         | 211A120123   | 1       |
| Gehe                    | Walnut leaf, cut         | 2111B151028  | 1       |
| Gehe                    | White deadnettle flower  | 3915-091     | 1       |
| Gehe                    | Wild pansy, cut          | 276259       | 1       |
| Gehe                    | Wormwood herb, cut       | 13381901     | 1       |
| Gehe                    | Yarrow flower, rubbed    | 12267702     | 2       |
| Gehe                    | Yarrow herb, cut         | 1128503      | 1       |
| GEHE                    | Burdock root, cut        | 10073213     | 2       |
| GEHE                    | Dexamphetamine sulfate   | 635J7FA70021 | 1       |
| GEHE                    | Dexamphetamine sulfate   | 635JFA70029  | 2       |
| GEHE                    | Dexamphetamine sulfate   | 12F11-N01    | 1       |
| GEHE                    | Equisetum stem, cut      | 270045       | 3       |
| GEHE                    | Hawthorn leaf with fl... | 1971A120215  | 8       |
| GEHE                    | Marshmallow root, pee... | 12145311     | 1       |
| GEHE                    | Methylrosanilinium ch... | 928104       | 1       |
| GEHE                    | Raspberry leaf, cut      | 272989       | 1       |
| GEHE                    | Rhubarb, cut             | 11321802     | 1       |
| GEHE                    | St. John's wort, cut     | 2477580      | 1       |
| GEHE                    | Thyme, rubbed            | 521205633    | 1       |
| GEHE                    | Trichloroacetic acid     | 10379406     | 2       |
| GEHE                    | Walnut leaf, cut         | 21022101/1   | 1       |
| GEHE                    | Yarrow herb, cut         | 11280514     | 4       |
| GEHE                    | Yarrow herb, cut         | 11306302     | 1       |
| Gehe / 08.03.13 Redwood | Blessed thistle, cut     | 205007       | 1       |
| Gehe 02.07.2013         | Raspberry leaf, cut      | 11030701     | 1       |
| Gehe 06.05.2013         | Matricaria flower        | 11169606     | 1       |
| Gehe 06.08.2013         | Raspberry leaf, cut      | 10013411     | 3       |
| gehe 07.12.2013         | Sage leaf, cut           | 2301/7120403 | 1       |
| Gehe 08.07.2013         | Aniseed                  | 1303780L     | 1       |
| Gehe 09.03.13           | Large waybread herb, ... | 12374104     | 10      |
| GEHE 10.03.2014         | Oak bark, cut            | 761A11816    | 1       |
| Gehe 10.05.2013         | Raspberry leaf, cut      | 2291A120507  | 9       |
| gehe 10.12.13           | Raspberry leaf, cut      | 229117121120 | 1       |
| Gehe 12.04.2013         | Fenugreek                | 12252602     | 4       |
| Gehe 12.04.2013         | Juniper, pounded         | 13020903     | 2       |
| Gehe 12.04.2013         | Tricalcium phosphate     | 12/13.N03    | 1       |
| Gehe 15.07.2013         | Aluminium chloride he... | 13022N09     | 1       |
| Gehe 18.12.12           | Dandelion root, cut      | 11003313     | 2       |
| Gehe 18.12.12           | Elecampane rhizome, cut  | 12113303     | 2       |
| gehe 20.11.13           | Fumitory, cut            | 3881B111013  | 2       |
| Gehe 21.05.2013         | Angelica root            | 278757       | 7       |
| Gehe 21.05.2013         | Tormentil                | 12040713     | 2       |
| gehe 21.08.2013         | Nettle root, cut         | 11265004     | 5       |

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| Supplier           | Substance                | Batch         | Spectra |
|--------------------|--------------------------|---------------|---------|
| Gehe 28.03.2013    | Aluminium potassium s... | 12184406      | 3       |
| Gehe 28.12.12      | Chelidonium majus her... | 3731A120611   | 5       |
| gehe 90.09.13      | Ginger, peeled           | 13100601      | 1       |
| Gehe am 14.01.2013 | Euphrasy herb, cut       | 270726        | 1       |
| Gehe am 27.03.2014 | Juniper, pounded         | 2890A130513   | 1       |
| gehe, 09.01.2013   | Elder flower, rubbed     | 1571A1202015  | 2       |
| gehe, 11.01.2013   | Mistletoe, cut           | 11294001      | 2       |
| Gehe08.06.2013     | Senna leaf, cut          | 2331-B-130241 | 2       |
| Großhandel         | Almonds, bitter, whole   | 40A100901     | 1       |
| Großhandel         | Angelica root            | 272721        | 1       |
| Großhandel         | Bitter orange flower ... | 11049213      | 1       |
| Großhandel         | Bitter orange flower ... | 12266606      | 1       |
| Großhandel         | Bitter orange flower ... | 12266607      | 1       |
| Großhandel         | Bitter orange flower ... | 12266610      | 1       |
| Großhandel         | Bitter orange flower ... | 12266612      | 1       |
| Großhandel         | Bitter orange flower ... | 12266602      | 3       |
| Großhandel         | Eleutherococcus, cut     | 10381816      | 1       |
| Großhandel         | Magnesium chloride he... | 12141807      | 4       |
| Großhandel         | Mallow flower, cut       | 1501B111215   | 2       |
| Großhandel         | Matricaria flower        | 1290A120403   | 4       |
| Großhandel         | Nutmeg                   | 7320A110825   | 1       |
| Großhandel         | Nutmeg                   | 7320A130911   | 1       |
| Großhandel         | Nystatin                 | 12158010      | 7       |
| Großhandel         | Passionflower herb, cut  | 12031706      | 4       |
| Großhandel         | Tall golden rod, cut     | 11280311      | 5       |
| Großhandel         | Thyme, rubbed            | 4622A12011    | 1       |
| Großhandel         | Valerian root, cut       | 12033809      | 13      |
| Gutenberg-Apotheke | Agnus castus fruit       | 61765         | 1       |
| Gutenberg-Apotheke | Aniseed                  | 1333902       | 1       |
| Gutenberg-Apotheke | Barberries               | 12217109      | 4       |
| Gutenberg-Apotheke | Elder berries            | 3010N120921   | 4       |
| Gutenberg-Apotheke | Nettle leaf, cut         | 18897         | 1       |
| Gutenberg-Apotheke | Raspberry leaf, cut      | 28911         | 1       |
| Haustee            | Mistletoe, cut           | 57010507      | 1       |
| HBK Gesundheit     | Maltodextrin             | 1143          | 4       |
| HBK Gesundheit     | Maltodextrin             | 2343          | 1       |
| Hedinger           | Dandelion herb with r... | 10121614      | 1       |
| Hedinger           | Linseed                  | 16011402      | 1       |
| Hedinger           | Magnesium sulfate hep... | 204037        | 1       |
| Hedinger           | Magnesium sulfate hep... | 204035        | 4       |
| Hedinger           | Rhubarb, powdered        | 13193110      | 1       |
| Hedinger/Phönix    | Sodium sulfate decahy... | 205025        | 2       |
| hepart ag          | Inositol hexanicotinate  | 63501         | 1       |
| Hepart AG          | Alchemilla, cut          | B-698kbA      | 1       |
| Hepart AG          | Alchemilla, cut          | 21963         | 3       |
| Hepart AG          | Aniseed                  | B216346, kbA  | 1       |
| Hepart AG          | Bitter fennel            | B492, kbA     | 1       |
| Hepart AG          | Bitter orange flower ... | B120822       | 1       |
| Hepart AG          | Black cumin seed         | 20720, kbA    | 1       |
| Hepart AG          | Blackthorn flower, ru... | N101109       | 2       |
| Hepart AG          | Buckwheat herb, cut      | B120509       | 2       |
| Hepart AG          | Caraway fruit            | B-224, kbA    | 1       |
| Hepart AG          | Daisy flower             | A130307       | 1       |
| Hepart AG          | Dill fruit               | L30057kbA     | 1       |
| Hepart AG          | Equisetum stem, cut      | B-695, kbA    | 1       |
| Hepart AG          | Fenugreek                | A120118       | 2       |
| Hepart AG          | Hawthorn flower          | 13010401      | 1       |
| Hepart AG          | Lavender flower          | A130214       | 4       |
| Hepart AG          | Male speedwell wort, ... | C130226       | 5       |
| Hepart AG          | Matricaria flower        | B-477, kbA    | 1       |

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| Supplier                  | Substance                | Batch       | Spectra |
|---------------------------|--------------------------|-------------|---------|
| Hepart AG                 | Melilot herb, cut        | A110324     | 6       |
| Hepart AG                 | Mullein flower, cut      | 12170904    | 3       |
| Hepart AG                 | Nettle leaf, cut         | P234605kbA  | 1       |
| Hepart AG                 | Primrose flower          | 11374403    | 3       |
| Hepart AG                 | Primrose flower          | 13086602    | 5       |
| Hepart AG                 | Restharrow root, cut     | B130404     | 3       |
| Hepart AG                 | Ribwort plantain, cut    | 20832       | 5       |
| Hepart AG                 | Robert herb, cut         | A110621     | 6       |
| Hepart AG                 | Savory, rubbed           | 12177205    | 3       |
| Hepart AG                 | St. John's wort, cut     | B-445, kbA  | 1       |
| Hepart AG                 | Stemless carline root    | B120726     | 1       |
| Hepart AG                 | Thyme, rubbed            | A130109     | 2       |
| Hepart AG                 | Walnut leaf, cut         | A120123     | 1       |
| Hepart AG                 | Willow bark, cut         | B100910     | 6       |
| Hepart AG                 | Willowherb, small flo... | 10326110    | 2       |
| Herbasinica               | Agrimony, cut            | 11374007    | 1       |
| Herbasinica               | Aluminium chloride he... | 11G05-N02   | 3       |
| Herbasinica               | Bitter fennel            | 1294710     | 1       |
| Herbasinica               | Black cohosh, cut        | nachprüfung | 1       |
| Herbasinica               | Blackthorn flower        | nachprüfung | 1       |
| Herbasinica               | Blue bottle flower wi... | nachprüfung | 1       |
| Herbasinica               | Chickweed, cut           | nachprüfung | 2       |
| Herbasinica               | Heavy alkaline bismut... | nachprüfung | 1       |
| Herbasinica               | Lavender flower          | nachprüfung | 1       |
| Herbasinica               | Lavender flower          | 1488A130830 | 1       |
| Herbasinica               | Magnesium sulfate hep... | 1303008-01  | 6       |
| Herbasinica               | Marian thistle fruit     | nachprüfung | 1       |
| Herbasinica               | Meadowsweet herb, cut    | 10381604    | 11      |
| Herbasinica               | Potassium hydroxide      | 11165708    | 2       |
| Herbasinica               | Primrose flower          | nachprüfung | 1       |
| Herbasinica               | Red-rose petal, cut      | nachprüfung | 1       |
| Herbasinica               | Rose mallow flower, cut  | nachprüfung | 1       |
| Herbasinica               | Sodium hydrogen carbo... | 12324704    | 5       |
| Herbasinica               | Tormentil                | nachprüfung | 3       |
| Hersteller: EuRho         | Nystatin                 | 1107036-01  | 8       |
| Hersteller: Klenf         | Coltsfoot leaf, cut      | 2021B120124 | 7       |
| himb                      | Birch leaf, cut          | 12193104    | 2       |
| HiperScan                 | Peppermint leaf, cut     |             | 2       |
| Hof-Apotheke, St. Afra    | Comfrey root             | 125041      | 1       |
| Hofmann Sommer            | Maté leaf, cut           | 2141a111213 | 3       |
| Holdermann                | Fuchsine                 | 11K18-N02   | 1       |
| Holdermann                | Tormentil                | 12040708    | 12      |
| holdermann euro           | Potassium hydrocarbon... | 1303002-01  | 5       |
| Hollborn                  | Bromothymol blue         | III13       | 1       |
| Hubertus Apotheke         | Equisetum stem, cut      | 3831C140403 | 1       |
| Ichthyol                  | Acorus root, peeled      | 272703      | 1       |
| Ichthyol/Phoenix          | Fenugreek, powdered      | 14377205    | 1       |
| ICHTHYOL-GESELLSCHAFT     | Sodium monohydrogenph... | Caelo       | 1       |
| Ichtyol/Phönix            | Alchemilla, cut          | 13141107    | 5       |
| Ichtyol/Phönix            | Zinc orotate dihydrate   | 12B02-N02   | 1       |
| Jenne                     | Aniseed                  | 2700A131015 | 3       |
| Jenne                     | Kaolin, heavy            | 13041803    | 3       |
| Jenne                     | Methadone hydrochloride  | 15B24-B02   | 1       |
| JENNE                     | Tragacanth, powdered     | 16110801    | 1       |
| Jinzhong Dongghui Phar... | Dimercaptosuccinic acid  | 121115      | 1       |
| k                         | Matricaria flower        | 1290A140513 | 1       |
| KBA Ware                  | Equisetum stem, cut      | 21879       | 6       |
| Kehr                      | Mallow flower, cut       | 10357908    | 3       |
| Kehr                      | Mullein flower, cut      | 11020901    | 1       |
| Kehr                      | Sodium monohydrogenph... | 11K30-N01   | 2       |

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| Supplier       | Substance                | Batch        | Spectra |
|----------------|--------------------------|--------------|---------|
| Kehr           | Stemless carline root    | 6191B1111205 | 1       |
| Kehr           | Zedoary root, cut        | 12125301     | 5       |
| Kenk / Phoenix | Calendula flower, cut    | 1241B130517  | 5       |
| Kenk / Phoenix | Daisy flower             | 1210A130307  | 4       |
| Kenk / Phoenix | Dandelion herb with r... | 6611B130321  | 31      |
| Kenk / Phoenix | European golden rod, ... | 1781B110826  | 1       |
| Kenk / Phoenix | Frangula bark, cut       | 661B110412   | 5       |
| Kenk / Phoenix | Hawthorn leaf with fl... | 1971A130307  | 5       |
| Kenk / Phoenix | Hop strobile             | 1451B130409  | 8       |
| Kenk / Phoenix | Juniper                  | 2890A120709  | 18      |
| Kenk / Phoenix | Lapacho wood, cut        | 5161A110204  | 1       |
| Kenk / Phoenix | Lavender flower          | 1489A130214  | 17      |
| Kenk / Phoenix | Lavender flower          | 1489A120103  | 27      |
| Kenk / Phoenix | Marian thistle herb, ... | 3701B120717  | 3       |
| Kenk / Phoenix | Melilot herb, cut        | 4151A110324  | 8       |
| Kenk / Phoenix | Raspberry leaf, cut      | 22781C120508 | 1       |
| Kenk / Phoenix | Rose hips with peel, ... | 2841B111019  | 3       |
| Kenk / Phoenix | Sage leaf, cut           | 2301A130904  | 1       |
| Kenk / Phoenix | St. John's wort, cut     | 4021A120604  | 23      |
| Kenk / Phoenix | Turmeric, javanese, cut  | 6731B130117  | 1       |
| Kle            | Dill fruit               | 2680A110204  | 1       |
| Klenk          | Abrotani herb, cut       | 3451A120312  | 21      |
| Klenk          | Abrotani herb, cut       | 26011403     | 1       |
| Klenk          | Abrotani herb, cut       | pzn4288802   | 1       |
| Klenk          | Abrotani herb, cut       | 3451a120312  | 2       |
| Klenk          | Abrotani herb, cut       | 21081301     | 1       |
| Klenk          | Acorus root, natural,... | B130807      | 1       |
| Klenk          | Acorus root, peeled      | 106212173    | 1       |
| Klenk          | Acorus root, peeled      | 6701b120301  | 1       |
| Klenk          | Acorus root, peeled      | 6701B130103  | 24      |
| Klenk          | Acorus root, peeled      | 6701B130870  | 1       |
| Klenk          | Acorus root, peeled      | 6701B120817  | 7       |
| Klenk          | Acorus root, peeled      | 6711B110606  | 1       |
| Klenk          | Acorus root, peeled      | 6701B120301  | 3       |
| Klenk          | Acorus root, peeled      | 6701B12031   | 1       |
| Klenk          | Acorus root, peeled      | 4797362      | 1       |
| Klenk          | Acorus root, peeled      | 6701B150407  | 1       |
| Klenk          | Acorus root, peeled      | 6701b130807  | 2       |
| Klenk          | Acorus root, peeled      | nachprüfung  | 1       |
| Klenk          | Acorus root, peeled      | 67001B1203   | 1       |
| Klenk          | Acorus root, peeled      | 6701b130103  | 2       |
| Klenk          | Agarikon                 | 1061a120312  | 1       |
| Klenk          | Agnus castus fruit       | A130613      | 1       |
| Klenk          | Agnus castus fruit       | A110614      | 3       |
| Klenk          | Agnus castus fruit       | 7110N150121  | 1       |
| Klenk          | Agnus castus fruit       | 7110N090701  | 1       |
| Klenk          | Agnus castus fruit       | 7110A130613  | 1       |
| Klenk          | Agnus castus fruit       | 12274007     | 3       |
| Klenk          | Agnus castus fruit       | A120803      | 1       |
| Klenk          | Agnus castus fruit       | 7110A110614  | 2       |
| Klenk          | Agrimony, cut            | 3481C120508  | 1       |
| Klenk          | Alchemilla, cut          | 3501B090417  | 1       |
| Klenk          | Alchemilla, cut          | 3501B100428  | 2       |
| Klenk          | Alchemilla, cut          | 3501A110301  | 4       |
| Klenk          | Alchemilla, cut          | 3501C121105  | 2       |
| Klenk          | Almonds, bitter, whole   | 40A120924    | 8       |
| Klenk          | Almonds, bitter, whole   | 40A111117    | 8       |
| Klenk          | Almonds, bitter, whole   | 40A111004    | 1       |
| Klenk          | Almonds, bitter, whole   | 40A0130909   | 1       |
| Klenk          | Almonds, bitter, whole   | 40A161028    | 1       |

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| Supplier | Substance                | Batch        | Spectra |
|----------|--------------------------|--------------|---------|
| Klenk    | Almonds, bitter, whole   | 40A150904    | 3       |
| Klenk    | Almonds, bitter, whole   | 40A130909    | 10      |
| Klenk    | Almonds, bitter, whole   | 40A140908    | 18      |
| Klenk    | Angelica root            | 6081N120110  | 19      |
| Klenk    | Angelica root            | 6081B130109  | 1       |
| Klenk    | Angelica root            | B130109      | 2       |
| Klenk    | Angelica root            | 6081n120110  | 1       |
| Klenk    | Angelica root            | 6081B130726  | 1       |
| Klenk    | Angelica root            | 6081B130410  | 3       |
| Klenk    | Angelica root            | 6081B150701  | 3       |
| Klenk    | Angelica root            | 6081B140918  | 1       |
| Klenk    | Angelica root            | 6081N100618  | 3       |
| Klenk    | Angelica root            | 6081b130109  | 2       |
| Klenk    | Angelica root            | 6081B130109  | 7       |
| Klenk    | Angelica root            | 6085B120614  | 1       |
| Klenk    | Angelica root            | 6082b130410  | 1       |
| Klenk    | Angelica root            | 6091B130109  | 1       |
| Klenk    | Aniseed                  | 1601211530   | 1       |
| Klenk    | Aniseed                  | 2700A110701  | 10      |
| Klenk    | Aniseed                  | 2700A120320  | 14      |
| Klenk    | Aniseed                  | 2901311530   | 1       |
| Klenk    | Aniseed                  | 212M-01530   | 1       |
| Klenk    | Aniseed                  | nachprüfung  | 1       |
| Klenk    | Aniseed                  | 2103311530   | 1       |
| Klenk    | Aniseed                  | 814Q01530    | 1       |
| Klenk    | Aniseed                  | 2700A-110701 | 1       |
| Klenk    | Aniseed                  | 2700a120320  | 1       |
| Klenk    | Aniseed                  | 2700A12107   | 1       |
| Klenk    | Aniseed                  | 2700A121107  | 1       |
| Klenk    | Aniseed                  | 3113Q01530   | 1       |
| Klenk    | Aniseed                  | 2700A150601  | 2       |
| Klenk    | Aniseed, pounded         | 2706B100120  | 1       |
| Klenk    | Aniseed, powdered        | 2704B110824  | 1       |
| Klenk    | Apple, cut               | A120302      | 3       |
| Klenk    | Arnica flower            | 1181B130605  | 1       |
| Klenk    | Artichoke leaf, cut      | 1981B130111  | 3       |
| Klenk    | Artichoke leaf, cut      | 1981B120413  | 1       |
| Klenk    | Artichoke leaf, cut      | 1981B121025  | 4       |
| Klenk    | Artichoke leaf, cut      | B121025      | 2       |
| Klenk    | Ash leaf, cut            | 5111A-01491  | 1       |
| Klenk    | Asparagus root, cut      | 6151B100332  | 1       |
| Klenk    | Asplenium scolopendri... | 4451B091116  | 1       |
| Klenk    | Asplenium scolopendri... | 4451B120605  | 1       |
| Klenk    | Barberry root bark, cut  | 551B120320   | 1       |
| Klenk    | Barberry root bark, cut  | 551B110128   | 6       |
| Klenk    | Basil, rubbed            | 3632A120502  | 5       |
| Klenk    | Basil, rubbed            | A120502      | 1       |
| Klenk    | Basil, rubbed            | 3632a120502  | 1       |
| Klenk    | Basil, rubbed            | A110201      | 1       |
| Klenk    | Bean shells, cut         | 171A110301   | 1       |
| Klenk    | Bean shells, cut         | 671C120321   | 16      |
| Klenk    | Bean shells, cut         | 671A110420   | 12      |
| Klenk    | Bean shells, cut         | 671C121105   | 8       |
| Klenk    | Bean shells, cut         | 671A110301   | 1       |
| Klenk    | Bean shells, cut         | 671A100816   | 2       |
| Klenk    | Bean shells, cut         | 671C130620   | 6       |
| Klenk    | Bean shells, cut         | 671A-110420  | 1       |
| Klenk    | Bean shells, cut         | C130620      | 1       |
| Klenk    | Bean shells, cut         | C120321      | 2       |
| Klenk    | Bean shells, cut         | C121105      | 2       |

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| Supplier | Substance             | Batch         | Spectra |
|----------|-----------------------|---------------|---------|
| Klenk    | Bean shells, cut      | 11030602      | 6       |
| Klenk    | Bean shells, cut      | 671A100420    | 1       |
| Klenk    | Bearberry leaf, cut   | 2391B130328   | 9       |
| Klenk    | Bearberry leaf, cut   | 2391B120314   | 9       |
| Klenk    | Bearberry leaf, cut   | 2391B120719   | 16      |
| Klenk    | Bearberry leaf, cut   | 23051202      | 1       |
| Klenk    | Bearberry leaf, cut   | 2391b120314   | 2       |
| Klenk    | Bearberry leaf, cut   | 2391B07030901 | 1       |
| Klenk    | Bilberry fruit, dried | 2910A090717   | 3       |
| Klenk    | Bilberry fruit, dried | N130131       | 2       |
| Klenk    | Bilberry fruit, dried | N121022       | 1       |
| Klenk    | Bilberry fruit, dried | 910N130131    | 2       |
| Klenk    | Bilberry fruit, dried | 2910N120921   | 3       |
| Klenk    | Bilberry fruit, dried | 2010N110304   | 1       |
| Klenk    | Bilberry fruit, dried | 2910n120921   | 1       |
| Klenk    | Bilberry fruit, dried | 2910n110304   | 1       |
| Klenk    | Bilberry fruit, dried | 2910n130131   | 1       |
| Klenk    | Bilberry fruit, dried | 2910N130131   | 11      |
| Klenk    | Bilberry fruit, dried | 2910N121022   | 8       |
| Klenk    | Bilberry leaf, cut    | 4042013       | 1       |
| Klenk    | Bilberry leaf, cut    | N110516       | 1       |
| Klenk    | Bilberry leaf, cut    | 2191N110516   | 5       |
| Klenk    | Birch leaf, cut       | 1901A-110726  | 3       |
| Klenk    | Birch leaf, cut       | A121130       | 2       |
| Klenk    | Birch leaf, cut       | 4213I01481    | 1       |
| Klenk    | Birch leaf, cut       | 4113A-01481   | 1       |
| Klenk    | Birch leaf, cut       | 1901A110726   | 36      |
| Klenk    | Birch leaf, cut       | 27121301      | 1       |
| Klenk    | Birch leaf, cut       | 1901A05051801 | 1       |
| Klenk    | Birch leaf, cut       | 28101306      | 1       |
| Klenk    | Birch leaf, cut       | 1901C120508   | 23      |
| Klenk    | Birch leaf, cut       | 21061303      | 1       |
| Klenk    | Birch leaf, cut       | 1901C12508    | 1       |
| Klenk    | Birch leaf, cut       | 20111201      | 1       |
| Klenk    | Birch leaf, cut       | 19121206      | 1       |
| Klenk    | Birch leaf, cut       | F-040413-1    | 1       |
| Klenk    | Birch leaf, cut       | C120802       | 1       |
| Klenk    | Birch leaf, cut       | 4021409       | 1       |
| Klenk    | Birch leaf, cut       | 1901A140214   | 1       |
| Klenk    | Birch leaf, cut       | 7021307       | 1       |
| Klenk    | Birch leaf, cut       | 1901c120508   | 3       |
| Klenk    | Birch leaf, cut       | 11101206      | 1       |
| Klenk    | Birch leaf, cut       | 1901A130318   | 2       |
| Klenk    | Birch leaf, cut       | 1901A121130   | 26      |
| Klenk    | Birch leaf, cut       | 1901A130218   | 5       |
| Klenk    | Birch leaf, cut       | 1901c120802   | 1       |
| Klenk    | Birch leaf, cut       | 1901C120802   | 25      |
| Klenk    | Birch leaf, cut       | 1901C-120508  | 1       |
| Klenk    | Bitter fennel         | 2860A13       | 1       |
| Klenk    | Bitter fennel         | 2866B130206   | 1       |
| Klenk    | Bitter fennel         | 2860A140612   | 10      |
| Klenk    | Bitter fennel         | 2860A120412   | 29      |
| Klenk    | Bitter fennel         | 2860A140613   | 1       |
| Klenk    | Bitter fennel         | 2866B100211   | 1       |
| Klenk    | Bitter fennel         | 2860A140224   | 2       |
| Klenk    | Bitter fennel         | 2860A150320   | 5       |
| Klenk    | Bitter fennel         | 2860a120412   | 3       |
| Klenk    | Bitter fennel         | 3812A-01545   | 1       |
| Klenk    | Bitter fennel         | 2860A130226   | 9       |
| Klenk    | Bitter fennel         | 2880A100503   | 2       |

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| Supplier | Substance                | Batch        | Spectra |
|----------|--------------------------|--------------|---------|
| Klenk    | Bitter fennel            | 2866B110318  | 2       |
| Klenk    | Bitter fennel            | 2860A140224  | 1       |
| Klenk    | Bitter fennel            | 2880N120418  | 4       |
| Klenk    | Bitter fennel            | 2860A130513  | 2       |
| Klenk    | Bitter fennel            | 2860,A150617 | 1       |
| Klenk    | Bitter orange flower ... | 1201B120822  | 1       |
| Klenk    | Bitter orange flower ... | 1201B110809  | 1       |
| Klenk    | Bitter orange flower ... | 3613m-01445  | 1       |
| Klenk    | Bitter orange peel, cut  | 531A091125   | 1       |
| Klenk    | Bitter orange peel, cut  | 2711B111207  | 1       |
| Klenk    | Bitter orange peel, cut  | 511B120830   | 7       |
| Klenk    | Bitter orange peel, cut  | 511C130226   | 1       |
| Klenk    | Bitter orange peel, cut  | 511B110321   | 4       |
| Klenk    | Bitter orange peel, cut  | C130226      | 3       |
| Klenk    | Bitter orange peel, cut  | B120830      | 1       |
| Klenk    | Bitter orange peel, cut  | 3613M-01531  | 1       |
| Klenk    | Bitter orange peel, cut  | 511c130226   | 1       |
| Klenk    | Black cohosh, cut        | 6721b130528  | 1       |
| Klenk    | Black cohosh, cut        | 6721B141202  | 1       |
| Klenk    | Black cohosh, cut        | 6721B081208  | 1       |
| Klenk    | Black cohosh, cut        | 6721B1130528 | 1       |
| Klenk    | Black cohosh, cut        | 3794377      | 1       |
| Klenk    | Black cohosh, cut        | 6721B130214  | 10      |
| Klenk    | Black cohosh, cut        | 6721B130528  | 5       |
| Klenk    | Black cohosh, cut        | B130528      | 2       |
| Klenk    | Black cumin seed         | A120703      | 1       |
| Klenk    | Black cumin seed         | 7330A120703  | 1       |
| Klenk    | Black mustard seed       | 7430A120813  | 2       |
| Klenk    | Black mustard seed, p... | A130422      | 1       |
| Klenk    | Black mustard seed, p... | 7434A120712  | 1       |
| Klenk    | Black mustard seed, p... | 7434A130422  | 3       |
| Klenk    | Black mustard seed, p... | 7434a150608  | 1       |
| Klenk    | Black mustard seed, p... | 7434A140923  | 2       |
| Klenk    | Black mustard seed, p... | 7434A150608  | 4       |
| Klenk    | Black pepper             | A130415      | 2       |
| Klenk    | Blackberry leaf, cut     | 101364009    | 1       |
| Klenk    | Blackberry leaf, cut     | 2271B111216  | 1       |
| Klenk    | Blackcurrant leaf, cut   | 2251a110204  | 1       |
| Klenk    | Blackcurrant leaf, cut   | 22511A110204 | 1       |
| Klenk    | Blackcurrant leaf, cut   | 2251A110204  | 4       |
| Klenk    | Blackcurrants            | 2990A110620  | 1       |
| Klenk    | Blackcurrants            | A121106      | 1       |
| Klenk    | Blackthorn flower        | 2612E-01468  | 1       |
| Klenk    | Blackthorn flower, ru... | 1150N101109  | 3       |
| Klenk    | Blackthorn flower, ru... | 1150n101109  | 1       |
| Klenk    | Blessed thistle, cut     | A110517      | 1       |
| Klenk    | Blessed thistle, cut     | nachprüfung  | 1       |
| Klenk    | Blue bottle flower wi... |              | 1       |
| Klenk    | Bogbean leaf, cut        | 2371A110809  | 3       |
| Klenk    | Bogbean leaf, cut        | 2371A100915  | 1       |
| Klenk    | Boldo leaf, cut          | 1911A100714  | 8       |
| Klenk    | Boldo leaf, cut          | 1911B090709  | 1       |
| Klenk    | Buckwheat herb, cut      | 4581B120509  | 3       |
| Klenk    | Burdock root, cut        | A120206      | 1       |
| Klenk    | Burdock root, cut        | 6161A101206  | 3       |
| Klenk    | Burdock root, cut        | 6161A-120103 | 1       |
| Klenk    | Burdock root, cut        | A130214      | 1       |
| Klenk    | Burdock root, cut        | 6161A120208  | 3       |
| Klenk    | Burdock root, cut        | 6161A080709  | 1       |
| Klenk    | Burdock root, cut        | 6161a120103  | 1       |

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| Supplier | Substance                | Batch        | Spectra |
|----------|--------------------------|--------------|---------|
| Klenk    | Burdock root, cut        | 6161A-101206 | 1       |
| Klenk    | Burdock root, cut        | 6161A120103  | 1       |
| Klenk    | Calendula flower         | 1250A110511  | 1       |
| Klenk    | Calendula flower         | 1241B130517  | 1       |
| Klenk    | Calendula flower         | 1241B120312  | 1       |
| Klenk    | Calendula flower         | C120321      | 1       |
| Klenk    | Calendula flower, cut    | 1241B110118  | 2       |
| Klenk    | Calendula flower, cut    | 1240A110418  | 2       |
| Klenk    | Calendula flower, cut    | 1241B120419  | 3       |
| Klenk    | Calendula flower, cut    | 1241N151209  | 1       |
| Klenk    | Calendula flower, cut    | B130517      | 2       |
| Klenk    | Calendula flower, cut    | 3013E1448    | 1       |
| Klenk    | Calendula flower, cut    | 2000234      | 1       |
| Klenk    | Calendula flower, cut    | 112211448    | 1       |
| Klenk    | Calendula flower, cut    | 204311448    | 1       |
| Klenk    | Calendula flower, cut    | 1241B130321  | 6       |
| Klenk    | Calendula flower, cut    | 1241B130927  | 1       |
| Klenk    | Calendula flower, cut    | 1241B160530  | 1       |
| Klenk    | Calendula flower, cut    | 1241B150902  | 1       |
| Klenk    | Calendula flower, cut    | 1241B140211  | 1       |
| Klenk    | Caraway fruit            | 2770A131008  | 4       |
| Klenk    | Caraway fruit            | 1810A-01537  | 1       |
| Klenk    | Caraway fruit            | nachprüfung  | 2       |
| Klenk    | Caraway fruit            | 2270A130521  | 1       |
| Klenk    | Caraway fruit            | 2770A110601  | 16      |
| Klenk    | Caraway fruit            | 2770A110818  | 8       |
| Klenk    | Caraway fruit            | 2770A120403  | 16      |
| Klenk    | Caraway fruit            | 2770A130521  | 12      |
| Klenk    | Caraway fruit            | 2770A120905  | 8       |
| Klenk    | Caraway fruit            | 2770a120905  | 2       |
| Klenk    | Caraway fruit            | 412091-1-P   | 1       |
| Klenk    | Caraway fruit            | 3712I-1537   | 1       |
| Klenk    | Caraway fruit            | 2770A130910  | 1       |
| Klenk    | Caraway fruit            | 5213A1537    | 1       |
| Klenk    | Caraway fruit            | A120905      | 3       |
| Klenk    | Caraway fruit            | 2770A140708  | 1       |
| Klenk    | Cardamom fruit           | A110810      | 3       |
| Klenk    | Cardamom fruit           | 2750A110810  | 2       |
| Klenk    | Cardamom fruit           | A130807      | 1       |
| Klenk    | Centaury, cut            | 3711B-111216 | 1       |
| Klenk    | Centaury, cut            | B120628      | 1       |
| Klenk    | Centaury, cut            | 3711B111216  | 2       |
| Klenk    | Ceylon cinnamon, fine... | 614B121024   | 4       |
| Klenk    | Ceylon cinnamon, fine... | 614b121024   | 1       |
| Klenk    | Ceylon cinnamon, fine... | 615B130325   | 3       |
| Klenk    | Ceylon cinnamon, fine... | 614a120411   | 1       |
| Klenk    | Ceylon cinnamon, fine... | 611B100628   | 1       |
| Klenk    | Ceylon cinnamon, fine... | 614B120411   | 2       |
| Klenk    | Ceylon cinnamon, fine... | 614B150422   | 1       |
| Klenk    | Ceylon cinnamon, fine... | 614B151008   | 2       |
| Klenk    | Ceylon cinnamon, fine... | 614B121010   | 2       |
| Klenk    | Chelidonium majus her... | 3731A130904  | 4       |
| Klenk    | Chelidonium majus her... | nachprüfung  | 1       |
| Klenk    | Chelidonium majus her... | 1406111632   | 1       |
| Klenk    | Chelidonium majus her... | 4711E-01632  | 1       |
| Klenk    | Chelidonium majus her... | 3731B100205  | 1       |
| Klenk    | Chelidonium majus her... | 3731A110301  | 12      |
| Klenk    | Chelidonium majus her... | 3731A-110301 | 1       |
| Klenk    | Chelidonium majus her... | 3731K120904  | 5       |
| Klenk    | Chickweed, cut           | 4551B090528  | 1       |

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| Supplier | Substance                | Batch        | Spectra |
|----------|--------------------------|--------------|---------|
| Klenk    | Chickweed, cut           | 4551b110222  | 1       |
| Klenk    | Chicory herb, cut        | 3751A080902  | 1       |
| Klenk    | Chicory herb, cut        | 3751A120307  | 5       |
| Klenk    | Chicory herb, cut        | 3751A-100118 | 1       |
| Klenk    | Chicory herb, cut        | 3751a120307  | 1       |
| Klenk    | Chicory herb, cut        | 3751c120614  | 1       |
| Klenk    | Chicory herb, cut        | 4510I-01634  | 1       |
| Klenk    | Chicory herb, cut        | A120123      | 2       |
| Klenk    | Chicory herb, cut        | 3751A100118  | 1       |
| Klenk    | Chicory herb, cut        | 3751A120123  | 4       |
| Klenk    | Chicory root, cut        | A130304      | 1       |
| Klenk    | Chicory root, cut        | 66221A101202 | 1       |
| Klenk    | Chicory root, cut        | 6221A090311  | 2       |
| Klenk    | Chicory root, cut        | 6221A101202  | 6       |
| Klenk    | Chicory root, cut        | 6221A130304  | 1       |
| Klenk    | Chicory root, cut        | 6221N130201  | 1       |
| Klenk    | Cinchona bark, cut       | 601B130415   | 1       |
| Klenk    | Cinchona bark, cut       | 601B130415   | 1       |
| Klenk    | Cinnamon rods (Ceylon... | A101018      | 1       |
| Klenk    | Cinnamon rods (Ceylon... | 610A101018   | 1       |
| Klenk    | Cinnamon rods (Ceylon... | B121016      | 1       |
| Klenk    | Cinnamon, cut            | 610A130927   | 1       |
| Klenk    | Cinnamon, cut            | 610A101018   | 1       |
| Klenk    | Clove                    | 1260A120328  | 6       |
| Klenk    | Clove                    | 1260A100617  | 2       |
| Klenk    | Clove                    | A120328      | 1       |
| Klenk    | Clove                    | pzn03485222  | 1       |
| Klenk    | Clove                    | 1260A101223  | 2       |
| Klenk    | Clove                    | pzn3485222   | 1       |
| Klenk    | Clove                    | PZN03485222  | 1       |
| Klenk    | Clove                    | 1260A110608  | 6       |
| Klenk    | Clove                    | 1260A130903  | 3       |
| Klenk    | Clove                    | 1260A150304  | 2       |
| Klenk    | Coltsfoot leaf, cut      | 2021B121203  | 6       |
| Klenk    | Coltsfoot leaf, cut      | 2021C140730  | 2       |
| Klenk    | Coltsfoot leaf, cut      | 2021B140131  | 2       |
| Klenk    | Coltsfoot leaf, cut      | 2021B130319  | 6       |
| Klenk    | Coltsfoot leaf, cut      | 2021B150407  | 1       |
| Klenk    | Coltsfoot leaf, cut      | 2021b121204  | 1       |
| Klenk    | Coltsfoot leaf, cut      | 2021B120601  | 5       |
| Klenk    | Coltsfoot leaf, cut      | 2012B120124  | 1       |
| Klenk    | Coltsfoot leaf, cut      | 2021B111111  | 5       |
| Klenk    | Coltsfoot leaf, cut      | B130227      | 1       |
| Klenk    | Coltsfoot leaf, cut      | B120124      | 1       |
| Klenk    | Coltsfoot leaf, cut      | 20021301     | 1       |
| Klenk    | Coltsfoot leaf, cut      | 14111302     | 1       |
| Klenk    | Coltsfoot leaf, cut      | 11101202     | 1       |
| Klenk    | Coltsfoot leaf, cut      | 8061207      | 1       |
| Klenk    | Coltsfoot leaf, cut      | 5122013a     | 1       |
| Klenk    | Coltsfoot leaf, cut      | 5011301      | 1       |
| Klenk    | Coltsfoot leaf, cut      | 23121302     | 1       |
| Klenk    | Coltsfoot leaf, cut      | 2021C130326  | 11      |
| Klenk    | Coltsfoot leaf, cut      | 26091301     | 1       |
| Klenk    | Coltsfoot leaf, cut      | 2021B111005  | 2       |
| Klenk    | Coltsfoot leaf, cut      | 2020B120124  | 1       |
| Klenk    | Coltsfoot leaf, cut      | KS100061     | 1       |
| Klenk    | Comfrey herb, cut        | 4561B100518  | 2       |
| Klenk    | Comfrey root             | 6241B120531  | 4       |
| Klenk    | Comfrey root             | 6241B130724  | 7       |
| Klenk    | Comfrey root             | 6241B130312  | 3       |

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| Supplier | Substance                | Batch         | Spectra |
|----------|--------------------------|---------------|---------|
| Klenk    | Comfrey root             | 6241B130619   | 8       |
| Klenk    | Comfrey root             | 6241B100715   | 1       |
| Klenk    | Comfrey root             | 6241b130724   | 2       |
| Klenk    | Comfrey root             | 6241b130619   | 1       |
| Klenk    | Comfrey root             | 6241B121214   | 2       |
| Klenk    | Comfrey root             | 6241b120807   | 1       |
| Klenk    | Comfrey root             | 6241B120807   | 4       |
| Klenk    | Comfrey root             | 6244B130624   | 1       |
| Klenk    | Comfrey root             | B130619       | 1       |
| Klenk    | Comfrey root             | 6241B06110202 | 1       |
| Klenk    | Comfrey root             | 6241B131009   | 1       |
| Klenk    | Comfrey root             | 6241B110811   | 1       |
| Klenk    | Common wormwood herb,... | 2591A130218   | 1       |
| Klenk    | Common wormwood herb,... | 3591A120123   | 7       |
| Klenk    | Common wormwood herb,... | 3591a120123   | 1       |
| Klenk    | Common wormwood herb,... | 12016708      | 6       |
| Klenk    | Common wormwood herb,... | A120123       | 2       |
| Klenk    | Common wormwood herb,... | 7312754       | 1       |
| Klenk    | Common wormwood herb,... | 12016707      | 5       |
| Klenk    | Common wormwood herb,... | 3591A11119    | 1       |
| Klenk    | Common wormwood herb,... | 3591A130218   | 9       |
| Klenk    | Common wormwood herb,... | 3591a130218   | 2       |
| Klenk    | Coriander                | 2790a121023   | 1       |
| Klenk    | Coriander                | A121023       | 3       |
| Klenk    | Coriander                | 2790A130129   | 2       |
| Klenk    | Coriander                | 2790A151117   | 1       |
| Klenk    | Coriander                | 2709A130129   | 1       |
| Klenk    | Coriander                | 2790A121023   | 9       |
| Klenk    | Cottonwood bud           | 3260A120828   | 1       |
| Klenk    | Couch grass rhizome, ... | 6781N111019   | 1       |
| Klenk    | Cowberry leaf, cut       | 2431B101006   | 2       |
| Klenk    | Daisy flower             | 1210a071301   | 1       |
| Klenk    | Daisy flower             | 1210A110223   | 1       |
| Klenk    | Daisy flower             | A130705       | 1       |
| Klenk    | Daisy flower             | 1210A120215   | 5       |
| Klenk    | Damiana leaf, cut        | 1990A130206   | 1       |
| Klenk    | Damiana leaf, cut        | 12064101      | 1       |
| Klenk    | Damiana leaf, cut        | A130206       | 2       |
| Klenk    | Dandelion herb with r... | 5122013b      | 1       |
| Klenk    | Dandelion herb with r... | 6611A110104   | 1       |
| Klenk    | Dandelion herb with r... | 6611B110104   | 7       |
| Klenk    | Dandelion herb with r... | 6611B130314   | 4       |
| Klenk    | Dandelion herb with r... | 6611B090306   | 1       |
| Klenk    | Dandelion herb with r... | 6611b110929   | 2       |
| Klenk    | Dandelion herb with r... | 6611B-120620  | 1       |
| Klenk    | Dandelion herb with r... | 6611B1104104  | 1       |
| Klenk    | Dandelion herb with r... | 6611B420620   | 1       |
| Klenk    | Dandelion herb with r... | 6611B-131206  | 1       |
| Klenk    | Dandelion herb with r... | 6611B160613   | 1       |
| Klenk    | Dandelion herb with r... | 6611B110929   | 3       |
| Klenk    | Dandelion herb with r... | 6611b131206   | 1       |
| Klenk    | Dandelion root, cut      | 6621A140114   | 4       |
| Klenk    | Dandelion root, cut      | 6621A140114   | 3       |
| Klenk    | Dandelion root, cut      | 6621A160111   | 1       |
| Klenk    | Dandelion root, cut      | 6621B151029   | 1       |
| Klenk    | Dandelion root, cut      | 6621A141027   | 2       |
| Klenk    | Dandelion root, cut      | 6621A110420   | 5       |
| Klenk    | Dandelion root, cut      | 6621A120606   | 22      |
| Klenk    | Dandelion root, cut      | 6101202       | 1       |
| Klenk    | Dandelion root, cut      | 6621N130813   | 8       |

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| <b>Supplier</b> | <b>Substance</b>        | <b>Batch</b>   | <b>Spectra</b> |
|-----------------|-------------------------|----------------|----------------|
| Klenk           | Dandelion root, cut     | 4513A-07035    | 1              |
| Klenk           | Dandelion root, cut     | A120606        | 1              |
| Klenk           | Dandelion root, cut     | 6621A120208    | 10             |
| Klenk           | Dandelion root, cut     | N130813        | 1              |
| Klenk           | Devil's claw root       | 6331B130129    | 5              |
| Klenk           | Devil's claw root       | 10111204       | 1              |
| Klenk           | Devil's claw root       | 6331B120508    | 4              |
| Klenk           | Dill fruit              | 2680a120312    | 1              |
| Klenk           | Dill fruit              | 2680A130806    | 1              |
| Klenk           | Dill fruit              | 2680A-120312   | 1              |
| Klenk           | Dill fruit              | A120312        | 1              |
| Klenk           | Dill fruit              | 2680A120312    | 8              |
| Klenk           | Dill herb, cut          | 3531B110726    | 1              |
| Klenk           | Elder flower, rubbed    | 1571A130930    | 3              |
| Klenk           | Elder flower, rubbed    | 1571a1211      | 1              |
| Klenk           | Elder flower, rubbed    | 157A120215     | 1              |
| Klenk           | Elder flower, rubbed    | 1571a121022    | 3              |
| Klenk           | Elder flower, rubbed    | 16061201       | 1              |
| Klenk           | Elder flower, rubbed    | 1571a120215    | 1              |
| Klenk           | Elder flower, rubbed    | 21091201       | 1              |
| Klenk           | Elder flower, rubbed    | 1571A121121    | 23             |
| Klenk           | Elder flower, rubbed    | 1571A121022    | 19             |
| Klenk           | Elder flower, rubbed    | 1021304        | 1              |
| Klenk           | Elder flower, rubbed    | 1571a121121    | 2              |
| Klenk           | Elder flower, rubbed    | 1571A130627    | 2              |
| Klenk           | Elder flower, rubbed    | 1571A-110223   | 1              |
| Klenk           | Elder flower, rubbed    | 1571A110223    | 20             |
| Klenk           | Elder flower, rubbed    | 1901211471     | 1              |
| Klenk           | Elder flower, rubbed    | 1571A110125    | 4              |
| Klenk           | Elder flower, rubbed    | A121121        | 1              |
| Klenk           | Elder flower, rubbed    | A120215        | 1              |
| Klenk           | Elder flower, rubbed    | 13021301       | 1              |
| Klenk           | Elder flower, rubbed    | 26061201       | 1              |
| Klenk           | Elder flower, rubbed    | 1571A120215    | 8              |
| Klenk           | Elder flower, rubbed    | 1571A141126    | 1              |
| Klenk           | Elder root, cut         | 6281B110427    | 4              |
| Klenk           | Elecampane rhizome, cut | 6341B100426    | 4              |
| Klenk           | Elecampane rhizome, cut | 6311141B130423 | 1              |
| Klenk           | Elecampane rhizome, cut | 6341B120611    | 2              |
| Klenk           | Elecampane rhizome, cut | B130423        | 3              |
| Klenk           | Elecampane rhizome, cut | 6341B130423    | 3              |
| Klenk           | Eleutherococcus, cut    | 7011A101206    | 1              |
| Klenk           | Eleutherococcus, cut    | 7011A110714    | 1              |
| Klenk           | Eleutherococcus, cut    | 7011A121204    | 1              |
| Klenk           | Elm bark, cut           | 841a120413     | 1              |
| Klenk           | Elm bark, cut           | 841A1101120    | 1              |
| Klenk           | Equisetum stem, cut     | 3831A120903    | 8              |
| Klenk           | Equisetum stem, cut     | 3831a120611    | 1              |
| Klenk           | Equisetum stem, cut     | 3831A-120726   | 1              |
| Klenk           | Equisetum stem, cut     | 3831A110922    | 2              |
| Klenk           | Equisetum stem, cut     | 3831C131104    | 1              |
| Klenk           | Equisetum stem, cut     | 3831A121018    | 6              |
| Klenk           | Equisetum stem, cut     | 3831A1230726   | 1              |
| Klenk           | Equisetum stem, cut     | 3831c131104    | 1              |
| Klenk           | Equisetum stem, cut     | 3831A120018    | 1              |
| Klenk           | Equisetum stem, cut     | 3831A11124     | 1              |
| Klenk           | Equisetum stem, cut     | 3831A120726    | 22             |
| Klenk           | Equisetum stem, cut     | 3831A120611    | 12             |
| Klenk           | Equisetum stem, cut     | 1804211642     | 1              |
| Klenk           | Equisetum stem, cut     | 3831A111124    | 8              |

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| Supplier | Substance                | Batch                | Spectra |
|----------|--------------------------|----------------------|---------|
| Klenk    | Equisetum stem, cut      | 3831A120529          | 13      |
| Klenk    | Equisetum stem, cut      | 4713U01642           | 1       |
| Klenk    | Equisetum stem, cut      | 4413Q1642            | 1       |
| Klenk    | Equisetum stem, cut      | 3831A110601          | 2       |
| Klenk    | Equisetum stem, cut      | 2213U01642           | 1       |
| Klenk    | Equisetum stem, cut      | 3831N110218          | 1       |
| Klenk    | Eucalyptus leaf, cut     | 2011B130306          | 4       |
| Klenk    | Eucalyptus leaf, cut     | 2011B120419          | 5       |
| Klenk    | Eucalyptus leaf, cut     | 2011b130306          | 1       |
| Klenk    | Eucalyptus leaf, cut     | 2011B110801          | 4       |
| Klenk    | Eucalyptus leaf, cut     | B120419              | 1       |
| Klenk    | Eucalyptus leaf, cut     | B130306              | 2       |
| Klenk    | Eucalyptus leaf, cut     | 2011B130306-35294110 | 1       |
| Klenk    | Euphrasy herb, cut       | 3871B130430          | 1       |
| Klenk    | Euphrasy herb, cut       | 15029806             | 1       |
| Klenk    | Euphrasy herb, cut       | 3871B100713          | 1       |
| Klenk    | Euphrasy herb, cut       | B130430              | 1       |
| Klenk    | Euphrasy herb, cut       | B101206              | 1       |
| Klenk    | European golden rod, ... | 1781B110706          | 2       |
| Klenk    | Fenugreek                | 7260A110530          | 19      |
| Klenk    | Fenugreek                | 9011301              | 1       |
| Klenk    | Fenugreek                | A130603              | 1       |
| Klenk    | Fenugreek                | 7260A120118          | 25      |
| Klenk    | Fenugreek                | 8061301              | 1       |
| Klenk    | Fenugreek                | 7260A130603          | 12      |
| Klenk    | Fenugreek, powdered      | 12082014A            | 1       |
| Klenk    | Fenugreek, powdered      | A110201              | 1       |
| Klenk    | Fenugreek, powdered      | 7264A110201          | 9       |
| Klenk    | Feverfew herb, cut       | 4831B110819          | 2       |
| Klenk    | Flax weed herb, cut      | 4011B121207          | 2       |
| Klenk    | Flax weed herb, cut      | 4011B131115          | 3       |
| Klenk    | Frangula bark, cut       | nachprüfung          | 1       |
| Klenk    | Frangula bark, cut       | 661B130306           | 1       |
| Klenk    | Frangula bark, cut       | 661B-110412          | 1       |
| Klenk    | Frangula bark, cut       | 661B-090903          | 1       |
| Klenk    | Frangula bark, cut       | pzn4266611           | 1       |
| Klenk    | Frangula bark, cut       | 6621B110412          | 1       |
| Klenk    | Fumitory, cut            | B120410              | 1       |
| Klenk    | Galeopsis herb, cut      | 3911A090219          | 2       |
| Klenk    | Galeopsis herb, cut      | 3911A130110          | 3       |
| Klenk    | Galeopsis herb, cut      | 3911A080409          | 1       |
| Klenk    | Galeopsis herb, cut      | 3911a130320          | 2       |
| Klenk    | Gentian root, cut        | 6311B140704          | 1       |
| Klenk    | Gentian root, cut        | 1911E-02142          | 1       |
| Klenk    | Gentian root, cut        | 6311B110509          | 1       |
| Klenk    | Gentian root, cut        | 6311B100817          | 2       |
| Klenk    | Gentian root, cut        | 6311A120723          | 4       |
| Klenk    | Gentian root, cut        | 6311a120723          | 2       |
| Klenk    | Gentian root, cut        | 6311B130205          | 2       |
| Klenk    | Geum urbanum herb, cut   | 3931B080714          | 2       |
| Klenk    | Ginger, peeled           | 6951B100302          | 1       |
| Klenk    | Ginger, peeled           | 6951B110822          | 2       |
| Klenk    | Ginger, peeled           | 6951B110119          | 1       |
| Klenk    | Ginger, peeled, powde... | 6954B110801          | 1       |
| Klenk    | Ginger, peeled, powde... | KS200260             | 1       |
| Klenk    | Ginger, peeled, powde... | 6954B160929          | 2       |
| Klenk    | Ginger, peeled, powde... | 6954B160429          | 5       |
| Klenk    | Ginger, peeled, powde... | 6954B121030          | 2       |
| Klenk    | Ginger, peeled, powde... | 6954B130418          | 2       |
| Klenk    | Ginger, peeled, powde... | B121030              | 2       |

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| Supplier | Substance                | Batch                | Spectra |
|----------|--------------------------|----------------------|---------|
| Klenk    | Ginkgo leaf, cut         | 2461A100429          | 10      |
| Klenk    | Ginkgo leaf, cut         | 2461B111108          | 1       |
| Klenk    | Goat's rue, cut          | 3901C110905          | 1       |
| Klenk    | Goat's rue, cut          | 3901B140801          | 1       |
| Klenk    | Ground ivy herb, cut     | 11052317             | 1       |
| Klenk    | Ground ivy herb, cut     | 3991B110304          | 3       |
| Klenk    | Ground ivy herb, cut     | 3991B130502          | 2       |
| Klenk    | Hamamelis leaf, cut      | B110214              | 1       |
| Klenk    | Hamamelis leaf, cut      | 2051B110214          | 1       |
| Klenk    | Hawthorn flower          | 1351B130819          | 3       |
| Klenk    | Hawthorn flower          | B1112107             | 1       |
| Klenk    | Hawthorn fruit           | 2806B110818          | 2       |
| Klenk    | Hawthorn fruit           | 2806B121203          | 2       |
| Klenk    | Hawthorn leaf with fl... | 1971A120813          | 26      |
| Klenk    | Hawthorn leaf with fl... | 1971A130307-35014110 | 1       |
| Klenk    | Hawthorn leaf with fl... | 1971A130307-3447     | 1       |
| Klenk    | Hawthorn leaf with fl... | 28101307             | 1       |
| Klenk    | Hawthorn leaf with fl... | 14101301             | 1       |
| Klenk    | Hawthorn leaf with fl... | A130307              | 1       |
| Klenk    | Hawthorn leaf with fl... | 1971A110620          | 7       |
| Klenk    | Hawthorn leaf with fl... | 1971a120215          | 1       |
| Klenk    | Hawthorn leaf with fl... | 1971a120727          | 1       |
| Klenk    | Hawthorn leaf with fl... | 1971A120813-34103101 | 1       |
| Klenk    | Hawthorn leaf with fl... | 1971a120813          | 2       |
| Klenk    | Hawthorn leaf with fl... | 1971A120727          | 14      |
| Klenk    | Hawthorn leaf with fl... | 20121302             | 1       |
| Klenk    | Hawthorn leaf with fl... | 1972A120727          | 1       |
| Klenk    | Hay flower               | A130304              | 1       |
| Klenk    | Hay flower               | 1400A120116          | 1       |
| Klenk    | Hay flower               | 10192103             | 1       |
| Klenk    | Heather flower, rubbed   | 13014202             | 1       |
| Klenk    | Henna powder             | 2074A111004          | 1       |
| Klenk    | Henna powder             | 20747A111004         | 1       |
| Klenk    | Hop strobile             | 1451B-120817         | 1       |
| Klenk    | Hop strobile             | 4301135              | 1       |
| Klenk    | Hop strobile             | 1450A110712          | 1       |
| Klenk    | Hop strobile             | 1451B130409          | 1       |
| Klenk    | Hop strobile             | 12008304             | 1       |
| Klenk    | Hop strobile             | 1451B111004          | 2       |
| Klenk    | Hop strobile             | 1451B140408          | 2       |
| Klenk    | Hop strobile             | B130409              | 1       |
| Klenk    | Hop strobile             | 1451b130107          | 1       |
| Klenk    | Hop strobile             | 1451B130107          | 6       |
| Klenk    | Hop strobile             | 20071301             | 1       |
| Klenk    | Hop strobile             | 1451b130409          | 1       |
| Klenk    | Hop strobile             | 1451B120817          | 12      |
| Klenk    | Horse chestnut flower... | 1440A110311          | 3       |
| Klenk    | Horse chestnut leaf, ... | 2551N130124          | 3       |
| Klenk    | Horse chestnut leaf, ... | 255100903            | 1       |
| Klenk    | Horse chestnut leaf, ... | 2551B081223          | 1       |
| Klenk    | Horse chestnut leaf, ... | 2551B111013          | 9       |
| Klenk    | Horse chestnut leaf, ... | N130124              | 2       |
| Klenk    | Iceland moss, cut        | 5191N110609          | 1       |
| Klenk    | Iceland moss, cut        | 5191A140828          | 1       |
| Klenk    | Ispaghula seed           | 7560A140203          | 4       |
| Klenk    | Ispaghula seed           | 7560A120330          | 1       |
| Klenk    | Ispaghula seed           | 7560A120828          | 6       |
| Klenk    | Ispaghula seed           | 20071302             | 1       |
| Klenk    | Ispaghula seed           | 7560A150420          | 3       |
| Klenk    | Ivy leaf, cut            | B130118              | 1       |

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| Supplier | Substance                | Batch             | Spectra |
|----------|--------------------------|-------------------|---------|
| Klenk    | Jasmine flower           | 1460A110505       | 1       |
| Klenk    | Java tea, cut            | 2221B12112        | 1       |
| Klenk    | Java tea, cut            | B110718           | 1       |
| Klenk    | Java tea, cut            | 2221B110718       | 11      |
| Klenk    | Java tea, cut            | B121112           | 3       |
| Klenk    | Java tea, cut            | 221B121112        | 1       |
| Klenk    | Java tea, cut            | 17121304          | 1       |
| Klenk    | Juniper                  | 2890A101201       | 8       |
| Klenk    | Juniper                  | 2890A100120       | 2       |
| Klenk    | Juniper                  | A120709           | 3       |
| Klenk    | Juniper                  | 2890A130513       | 2       |
| Klenk    | Juniper                  | 2890a120709       | 1       |
| Klenk    | Juniper, pounded         | 2896B121016       | 7       |
| Klenk    | Kaolin, heavy            | 424A130507        | 4       |
| Klenk    | Kaolin, heavy            | 424A100819        | 2       |
| Klenk    | Kaolin, heavy            | 424A130507        | 1       |
| Klenk    | Kaolin, heavy            | 45131I01190       | 1       |
| Klenk    | Kelp, cut                | 1051A110920       | 1       |
| Klenk    | Knotgrass, cut           | 140713a           | 1       |
| Klenk    | Knotgrass, cut           | 4301A120912       | 2       |
| Klenk    | Knotgrass, cut           | 4301A121120       | 3       |
| Klenk    | Ladys bedstraw herb,...  | 3921C120802       | 1       |
| Klenk    | Ladys bedstraw herb,...  | 3921C130226       | 1       |
| Klenk    | Ladys bedstraw herb,...  | 3921B101012       | 1       |
| Klenk    | Lapacho wood, cut        | 13298302          | 1       |
| Klenk    | Large waybread herb, ... | N111121           | 1       |
| Klenk    | Large waybread herb, ... | 4281N110404       | 1       |
| Klenk    | Large waybread herb, ... | 4281N111121       | 5       |
| Klenk    | Laurel leaf              | B110809           | 1       |
| Klenk    | Laurel leaf, cut         | B110809           | 2       |
| Klenk    | Lavender flower          | 1489A1203         | 1       |
| Klenk    | Lavender flower          | 1488A111201       | 2       |
| Klenk    | Lavender flower          | 1802211462        | 1       |
| Klenk    | Lavender flower          | 1489A100125       | 1       |
| Klenk    | Lavender flower          | 1488A120803       | 3       |
| Klenk    | Lavender flower          | 1488B130604       | 6       |
| Klenk    | Lavender flower          | 1137903           | 1       |
| Klenk    | Lavender flower          | 1489A120919       | 8       |
| Klenk    | Lavender flower          | 1489A1209019      | 1       |
| Klenk    | Lavender flower          | 1488B130111       | 2       |
| Klenk    | Lavender flower          | 313U-01462        | 1       |
| Klenk    | Lemon grass, cut         | 7721A130708       | 1       |
| Klenk    | Lemon grass, cut         | A120906           | 1       |
| Klenk    | Lemon grass, cut         | A130907           | 1       |
| Klenk    | Lemon grass, cut         | 7721A120906       | 1       |
| Klenk    | Lemon peel, cut          | 621A130221        | 1       |
| Klenk    | Lemon peel, cut          | B130521           | 1       |
| Klenk    | Lemon peel, cut          | 621A091016        | 3       |
| Klenk    | Lemon peel, cut          | A130221           | 3       |
| Klenk    | Lemon verbena leaf, cut  | 2411B110408       | 2       |
| Klenk    | Lime flower, cut         | 1611B110421       | 2       |
| Klenk    | Lime flower, cut         | 1611B11011        | 1       |
| Klenk    | Lime flower, cut         | B130905           | 4       |
| Klenk    | Lime flower, cut         | B130307           | 2       |
| Klenk    | Lime flower, cut         | Pr.Nr.4411A-01474 | 1       |
| Klenk    | Lime flower, cut         | 1611b121105       | 1       |
| Klenk    | Lime flower, cut         | 1611B121105       | 6       |
| Klenk    | Lime flower, cut         | 1611B111011       | 7       |
| Klenk    | Lime flower, cut         | 1611A12110        | 1       |
| Klenk    | Lime flower, cut         | 1611B130905       | 5       |

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| Supplier | Substance                | Batch          | Spectra |
|----------|--------------------------|----------------|---------|
| Klenk    | Lime flower, cut         | 1611B130307    | 3       |
| Klenk    | Lime flower, cut         | 1611B1010004   | 1       |
| Klenk    | Lime flower, cut         | 1611B131220    | 1       |
| Klenk    | Lime flower, cut         | 1611a121120    | 2       |
| Klenk    | Lime flower, cut         | 1611A121120    | 11      |
| Klenk    | Linseed                  | A130110        | 1       |
| Klenk    | Linseed                  | 7308A150710    | 2       |
| Klenk    | Linseed                  | 7307A140605    | 1       |
| Klenk    | Linseed                  | 7308A100705    | 1       |
| Klenk    | Linseed                  | 7308A130110    | 5       |
| Klenk    | Linseed                  | 7307A141201    | 6       |
| Klenk    | Linseed                  | 7300a130110    | 1       |
| Klenk    | Linseed                  | 7307A170111    | 1       |
| Klenk    | Linseed                  | 737A130722     | 1       |
| Klenk    | Linseed                  | 7307A140526    | 3       |
| Klenk    | Linseed                  | 7500A140556    | 1       |
| Klenk    | Linseed                  | 7300A130722    | 9       |
| Klenk    | Linseed                  | 7308A111107    | 5       |
| Klenk    | Linseed                  | 7307A-130722   | 1       |
| Klenk    | Linseed                  | 7397A140605    | 1       |
| Klenk    | Linseed                  | 1910212240     | 1       |
| Klenk    | Linseed                  | 7307A130110    | 18      |
| Klenk    | Linseed                  | 7307A150710    | 5       |
| Klenk    | Linseed                  | 7307A131104    | 14      |
| Klenk    | Linseed                  | 7307A131021    | 1       |
| Klenk    | Linseed                  | 7307A121212    | 2       |
| Klenk    | Linseed                  | 7307A160414    | 1       |
| Klenk    | Linseed                  | 7300A130110    | 9       |
| Klenk    | Linseed                  | 7300A141201    | 3       |
| Klenk    | Linseed                  | 7300A100705    | 2       |
| Klenk    | Linseed                  | 7300A111107    | 6       |
| Klenk    | Linseed                  | 5615003        | 1       |
| Klenk    | Linseed                  | 1913Q-02240    | 1       |
| Klenk    | Linseed                  | 7307a131104    | 1       |
| Klenk    | Linseed                  | 7307a111107    | 1       |
| Klenk    | Linseed                  | 7307A130722    | 7       |
| Klenk    | Linseed                  | 903312240      | 1       |
| Klenk    | Linseed                  | 7307A130124    | 2       |
| Klenk    | Linseed                  | 2002285        | 1       |
| Klenk    | Linseed                  | 3707A140526    | 1       |
| Klenk    | Linseed                  | 7307A-130110   | 1       |
| Klenk    | Liquorice root, peeled   | A130426        | 1       |
| Klenk    | Liquorice root, peeled   | 6381A140109    | 2       |
| Klenk    | Liquorice root, peeled   | 6381A130426    | 22      |
| Klenk    | Liquorice root, peeled   | 6381a121126    | 1       |
| Klenk    | Liquorice root, peeled   | 6381A120806    | 5       |
| Klenk    | Liquorice root, peeled   | 6281a120611    | 1       |
| Klenk    | Liquorice root, peeled   | 6381a111004    | 1       |
| Klenk    | Liquorice root, peeled   | A130820        | 3       |
| Klenk    | Liquorice root, peeled   | 6381a120611    | 1       |
| Klenk    | Liquorice root, peeled   | 6381A120611    | 16      |
| Klenk    | Liquorice root, peeled   | 6381111A121126 | 1       |
| Klenk    | Liquorice root, peeled   | 6381A110531    | 2       |
| Klenk    | Liquorice root, peeled   | 638A130820     | 1       |
| Klenk    | Liquorice root, peeled   | 6381A111004    | 17      |
| Klenk    | Liquorice root, peeled   | 6381A130820    | 7       |
| Klenk    | Liquorice root, peeled   | 6381A121126    | 35      |
| Klenk    | Liquorice root, natur... | 6391A080905    | 5       |
| Klenk    | Liquorice root, natur... | 6391A110421    | 4       |
| Klenk    | Liquorice root, natur... | 6390A101020    | 1       |

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| Supplier | Substance                | Batch                | Spectra |
|----------|--------------------------|----------------------|---------|
| Klenk    | Lovage root, cut         | 6371A080508          | 5       |
| Klenk    | Lovage root, cut         | 6371B121029          | 3       |
| Klenk    | Lovage root, cut         | 6371b121029          | 2       |
| Klenk    | Lovage root, cut         | 6371B-121029         | 1       |
| Klenk    | Lovage root, cut         | B110228              | 1       |
| Klenk    | Lovage root, cut         | B121029              | 1       |
| Klenk    | Lungwort herb, cut       | 4331B111205          | 2       |
| Klenk    | Lungwort herb, cut       | 4331A120813          | 1       |
| Klenk    | Lycopodium herb, cut     | 4111B110428          | 2       |
| Klenk    | Maize style, cut         | A110411              | 1       |
| Klenk    | Maize style, cut         | 5581A111206          | 1       |
| Klenk    | Maize style, cut         | 5581A081204          | 1       |
| Klenk    | Male speedwell wort, ... | 4661c130226-34343111 | 1       |
| Klenk    | Male speedwell wort, ... | 4661C130226-32743106 | 1       |
| Klenk    | Male speedwell wort, ... | 4661C131104          | 1       |
| Klenk    | Male speedwell wort, ... | 6661C130226          | 1       |
| Klenk    | Male speedwell wort, ... | C120321              | 1       |
| Klenk    | Male speedwell wort, ... | nachprüfung          | 1       |
| Klenk    | Male speedwell wort, ... | 4661C13026           | 1       |
| Klenk    | Male speedwell wort, ... | 4661c120802          | 1       |
| Klenk    | Male speedwell wort, ... | 4661C-111011         | 1       |
| Klenk    | Male speedwell wort, ... | 4661C111011          | 20      |
| Klenk    | Male speedwell wort, ... | 4661C120802          | 14      |
| Klenk    | Male speedwell wort, ... | 4661C130226          | 29      |
| Klenk    | Male speedwell wort, ... | 4661c120321          | 1       |
| Klenk    | Male speedwell wort, ... | 4661A090318          | 1       |
| Klenk    | Male speedwell wort, ... | 4661B101011          | 1       |
| Klenk    | Male speedwell wort, ... | 4661B110916          | 2       |
| Klenk    | Male speedwell wort, ... | 4661C2004            | 1       |
| Klenk    | Mallow flower, cut       | 1501B100408          | 1       |
| Klenk    | Mallow flower, cut       | 1501B120427          | 11      |
| Klenk    | Mallow flower, cut       | 1501B110207          | 2       |
| Klenk    | Mallow flower, cut       | 1501b110207          | 1       |
| Klenk    | Mallow flower, cut       | 1501b111215          | 1       |
| Klenk    | Mallow flower, cut       | 150B111215           | 1       |
| Klenk    | Mallow flower, cut       | 1501B-120427         | 1       |
| Klenk    | Mallow flower, cut       | B120427              | 1       |
| Klenk    | Mallow flower, cut       | B130829              | 3       |
| Klenk    | Mallow flower, cut       | 1501B120508          | 6       |
| Klenk    | Mallow flower, cut       | 1501B130829          | 3       |
| Klenk    | Mallow flower, cut       | 1910211464           | 1       |
| Klenk    | Mallow leaf, cut         | B130225              | 1       |
| Klenk    | Mallow leaf, cut         | 2131B10529           | 1       |
| Klenk    | Mallow leaf, cut         | 2131B130225          | 4       |
| Klenk    | Mallow leaf, cut         | 2131B120529          | 7       |
| Klenk    | Mallow leaf, cut         | 2131B110420          | 4       |
| Klenk    | Manna, cut               | 5221A140210          | 4       |
| Klenk    | Manna, cut               | 5221A120509          | 9       |
| Klenk    | Manna, cut               | 5221A110314          | 1       |
| Klenk    | Manna, cut               | 5221A150107          | 1       |
| Klenk    | Marian thistle fruit     | 7180A132019          | 1       |
| Klenk    | Marian thistle fruit     | 6621A120606          | 1       |
| Klenk    | Marian thistle fruit     | 7180A120725          | 3       |
| Klenk    | Marian thistle fruit     | 7180A120207          | 2       |
| Klenk    | Marian thistle fruit     | 7180A090929          | 1       |
| Klenk    | Marian thistle fruit     | 70180A120725         | 1       |
| Klenk    | Marian thistle fruit     | 7180A130219          | 2       |
| Klenk    | Marian thistle fruit     | A120725              | 1       |
| Klenk    | Marian thistle herb, ... | 913E-01627           | 1       |
| Klenk    | Marian thistle herb, ... | 2011402              | 1       |

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| Supplier | Substance                | Batch        | Spectra |
|----------|--------------------------|--------------|---------|
| Klenk    | Marian thistle herb, ... | 3701a111207  | 1       |
| Klenk    | Marian thistle herb, ... | 3701A100916  | 2       |
| Klenk    | Marian thistle herb, ... | 3701B130318  | 6       |
| Klenk    | Marian thistle herb, ... | 3701B111117  | 1       |
| Klenk    | Marian thistle herb, ... | B110728      | 1       |
| Klenk    | Marian thistle herb, ... | 3701A111207  | 12      |
| Klenk    | Marian thistle herb, ... | 3701B110610  | 1       |
| Klenk    | Marian thistle herb, ... | 11041310     | 1       |
| Klenk    | Marjoram herb, rubbed    | 4881a101025  | 1       |
| Klenk    | Marjoram herb, rubbed    | 4881A1311105 | 1       |
| Klenk    | Marjoram herb, rubbed    | 12345678     | 1       |
| Klenk    | Marjoram herb, rubbed    | 4881A091119  | 1       |
| Klenk    | Marjoram herb, rubbed    | 4881A101025  | 17      |
| Klenk    | Marjoram herb, rubbed    | ohne         | 1       |
| Klenk    | Marjoram herb, rubbed    | A101025      | 2       |
| Klenk    | Marrubium vulgare her... | 4141A130110  | 1       |
| Klenk    | Marrubium vulgare her... | 13289102     | 1       |
| Klenk    | Marshmallow root, pee... | 6071B091207  | 1       |
| Klenk    | Marshmallow root, pee... | 6074B100416  | 1       |
| Klenk    | Marshmallow root, pee... | 6071A120306  | 4       |
| Klenk    | Marshmallow root, pee... | 8120         | 1       |
| Klenk    | Marshmallow root, pee... | 6071A120314  | 18      |
| Klenk    | Marshmallow root, pee... | A130408      | 3       |
| Klenk    | Marshmallow root, pee... | 6071B110329  | 1       |
| Klenk    | Marshmallow root, pee... | 130116       | 1       |
| Klenk    | Marshmallow root, pee... | 6071A120306  | 1       |
| Klenk    | Marshmallow root, pee... | 6071A-120314 | 1       |
| Klenk    | Marshmallow root, pee... | 6071a130408  | 1       |
| Klenk    | Marshmallow root, pee... | 6071B090311  | 1       |
| Klenk    | Maté leaf, cut           | 2141A120821  | 3       |
| Klenk    | Maté leaf, cut           | 2141A-101102 | 1       |
| Klenk    | Maté leaf, cut           | 2131A111213  | 1       |
| Klenk    | Matricaria flower        | 1290A130502  | 1       |
| Klenk    | Matricaria flower        | 1290A130516  | 3       |
| Klenk    | Matricaria flower        | 1290A110421  | 1       |
| Klenk    | Matricaria flower        | 27111209     | 1       |
| Klenk    | Matricaria flower        | 1290A120620  | 19      |
| Klenk    | Matricaria flower        | 1290B130415  | 41      |
| Klenk    | Matricaria flower        | 1290A120529  | 3       |
| Klenk    | Matricaria flower        | 1290A130516  | 9       |
| Klenk    | Matricaria flower        | 1290B140123  | 2       |
| Klenk    | Matricaria flower        | B130415      | 2       |
| Klenk    | Matricaria flower        | 2310211452   | 1       |
| Klenk    | Matricaria flower        | 4100113002   | 2       |
| Klenk    | Matricaria flower        | A120529      | 1       |
| Klenk    | Matricaria flower        | 1290A120601  | 14      |
| Klenk    | Matricaria flower        | A130516      | 1       |
| Klenk    | Matricaria flower        | 27111204     | 1       |
| Klenk    | Matricaria flower        | 1290B101122  | 1       |
| Klenk    | Matricaria flower        | 16121301     | 1       |
| Klenk    | Matricaria flower        | 14111314     | 1       |
| Klenk    | Matricaria flower        | 129A120620   | 1       |
| Klenk    | Matricaria flower        | 1290A20404   | 1       |
| Klenk    | Matricaria flower        | 1290A150618  | 1       |
| Klenk    | Matricaria flower        | 1290A130502  | 1       |
| Klenk    | Matricaria flower        | 1290A-120620 | 1       |
| Klenk    | Matricaria flower        | 1290A12061   | 1       |
| Klenk    | Matricaria flower        | 1290A110825  | 3       |
| Klenk    | Matricaria flower        | 11101302     | 1       |
| Klenk    | Matricaria flower        | A130502      | 1       |

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| Supplier | Substance                | Batch                | Spectra |
|----------|--------------------------|----------------------|---------|
| Klenk    | Matricaria flower        | A120529              | 1       |
| Klenk    | Matricaria flower        | 2701211452           | 1       |
| Klenk    | Matricaria flower        | 1290B130415          | 4       |
| Klenk    | Matricaria flower        | 1290A110607          | 3       |
| Klenk    | Matricaria flower        | 1290A120601          | 2       |
| Klenk    | Matricaria flower        | 1290A140508          | 1       |
| Klenk    | Matricaria flower        | 1290B140123          | 2       |
| Klenk    | Matricaria flower        | 1290B140624          | 1       |
| Klenk    | Matricaria flower        | 1290A120404          | 11      |
| Klenk    | Matricaria flower        | 1290A120404          | 1       |
| Klenk    | Matricaria flower        | 1290A120529          | 1       |
| Klenk    | Matricaria flower        | 1290a120620          | 1       |
| Klenk    | Meadowsweet flower, r... | ChB: 1581a120312     | 1       |
| Klenk    | Meadowsweet flower, r... | A120312              | 1       |
| Klenk    | Meadowsweet flower, r... | 1581A090713          | 1       |
| Klenk    | Meadowsweet herb, cut    | 4541A120313          | 2       |
| Klenk    | Melilot herb, cut        | 4151A120912          | 2       |
| Klenk    | Melissa leaf, cut        | 2161A121009/PN:1198  | 1       |
| Klenk    | Melissa leaf, cut        | 2161A111207          | 21      |
| Klenk    | Melissa leaf, cut        | 2161A130806          | 4       |
| Klenk    | Melissa leaf, cut        | 2161A120718          | 17      |
| Klenk    | Melissa leaf, cut        | 27091201             | 1       |
| Klenk    | Melissa leaf, cut        | 2161A151209          | 1       |
| Klenk    | Melissa leaf, cut        | 2161A121029          | 6       |
| Klenk    | Melissa leaf, cut        | 2161A121009          | 15      |
| Klenk    | Melissa leaf, cut        | 2161a111207          | 2       |
| Klenk    | Melissa leaf, cut        | 2161A121206          | 3       |
| Klenk    | Melissa leaf, cut        | 2161A110818          | 1       |
| Klenk    | Melissa leaf, cut        | 2161A101216          | 1       |
| Klenk    | Melissa leaf, cut        | 2161A110207          | 1       |
| Klenk    | Melissa leaf, cut        | 111207               | 1       |
| Klenk    | Melissa leaf, cut        | 2807211503           | 1       |
| Klenk    | Mistletoe, cut           | 4691A720507          | 1       |
| Klenk    | Mistletoe, cut           | 4691A120507          | 3       |
| Klenk    | Mistletoe, cut           | 4691a130307          | 2       |
| Klenk    | Mistletoe, cut           | 110816               | 1       |
| Klenk    | Mistletoe, cut           | 1512211695           | 1       |
| Klenk    | Mistletoe, cut           | 2901311695           | 1       |
| Klenk    | Mistletoe, cut           | 4691A110816          | 2       |
| Klenk    | Mistletoe, cut           | 4691A121122          | 12      |
| Klenk    | Mistletoe, cut           | 4691a110816          | 1       |
| Klenk    | Mistletoe, cut           | 4691A120419          | 9       |
| Klenk    | Mistletoe, cut           | 4691A-120507         | 1       |
| Klenk    | Mistletoe, cut           | 4691a121122          | 1       |
| Klenk    | Mistletoe, cut           | 4691A121122-35454110 | 1       |
| Klenk    | Mistletoe, cut           | 4961A120419          | 2       |
| Klenk    | Mistletoe, cut           | 603211695            | 1       |
| Klenk    | Mistletoe, cut           | 4691A130307          | 7       |
| Klenk    | Motherwort herb, cut     | 4071A-100707         | 1       |
| Klenk    | Mullein flower, cut      | 1651B121109          | 21      |
| Klenk    | Mullein flower, cut      | 1651B110203          | 2       |
| Klenk    | Mullein flower, cut      | 3951B121218          | 1       |
| Klenk    | Mullein flower, cut      | 1651B150722          | 1       |
| Klenk    | Mullein flower, cut      | 1651b130820          | 2       |
| Klenk    | Mullein flower, cut      | 1651b120315          | 1       |
| Klenk    | Mullein flower, cut      | 1651B120315          | 5       |
| Klenk    | Mullein flower, cut      | 1651B140324          | 2       |
| Klenk    | Mullein flower, cut      | 1650A120612          | 1       |
| Klenk    | Mullein flower, cut      | 1650A111018          | 3       |
| Klenk    | Mullein flower, cut      | 1650A100608          | 1       |

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| Supplier | Substance                | Batch        | Spectra |
|----------|--------------------------|--------------|---------|
| Klenk    | Mullein flower, cut      | 1651B110915  | 1       |
| Klenk    | Mullein flower, cut      | A120612      | 1       |
| Klenk    | Mullein flower, cut      | 1651B130820  | 5       |
| Klenk    | Mullein flower, cut      | 15651B121109 | 1       |
| Klenk    | Myrrh                    | 3351A160330  | 1       |
| Klenk    | Myrrh                    | 3351A121004  | 1       |
| Klenk    | Myrrh                    | 3351A100628  | 1       |
| Klenk    | Myrrh                    | 3351A120514  | 1       |
| Klenk    | Myrrh                    | 3351A130902  | 1       |
| Klenk    | Nettle leaf, cut         | 2381A-120619 | 1       |
| Klenk    | Nettle leaf, cut         | 2381A141124  | 1       |
| Klenk    | Nettle leaf, cut         | 2381A121010  | 2       |
| Klenk    | Nettle leaf, cut         | 2381a120619  | 4       |
| Klenk    | Nettle leaf, cut         | A110913      | 1       |
| Klenk    | Nettle leaf, cut         | 2381A130122  | 30      |
| Klenk    | Nettle leaf, cut         | 2381A120619  | 16      |
| Klenk    | Nettle leaf, cut         | 2381A-121010 | 1       |
| Klenk    | Nettle leaf, cut         | 2381a100818  | 1       |
| Klenk    | Nettle leaf, cut         | 2381A110913  | 30      |
| Klenk    | Nettle leaf, cut         | 2372A130703  | 1       |
| Klenk    | Nettle leaf, cut         | 2381A130703  | 16      |
| Klenk    | Nettle leaf, cut         | 2381a130122  | 1       |
| Klenk    | Nettle leaf, cut         | 1107211689   | 1       |
| Klenk    | Nettle leaf, cut         | 2381A150109  | 1       |
| Klenk    | Nettle leaf, cut         | 2381A151012  | 1       |
| Klenk    | Nettle leaf, cut         | 4513E3054    | 1       |
| Klenk    | Nettle leaf, cut         | 7470A111117  | 1       |
| Klenk    | Nettle leaf, cut         | A130122      | 1       |
| Klenk    | Nettle leaf, cut         | A130703      | 1       |
| Klenk    | Nettle leaf, cut         | 1913A-03054  | 1       |
| Klenk    | Nettle leaf, cut         | 114Q-03054   | 1       |
| Klenk    | Nettle leaf, cut         | 2381A110809  | 1       |
| Klenk    | Nettle leaf, cut         | 2381A140221  | 1       |
| Klenk    | Nettle root, cut         | 9931B120927  | 1       |
| Klenk    | Nettle root, cut         | nachprüfung  | 1       |
| Klenk    | Nettle root, cut         | 6631B120416  | 1       |
| Klenk    | Nettle root, cut         | 6631N110513  | 1       |
| Klenk    | Nettle seed              | 7470A110418  | 1       |
| Klenk    | Nettle seed              | 7470A160928  | 1       |
| Klenk    | Nettle seed              | 2021505      | 1       |
| Klenk    | Nettle seed              | 7470A151009  | 1       |
| Klenk    | Nettle seed              | 7470A141021  | 1       |
| Klenk    | Nutmeg, powdered (spi... | A130304      | 2       |
| Klenk    | Nutmeg, powdered (spi... | 7325a120903  | 1       |
| Klenk    | Nutmeg, powdered (spi... | 7325A130515  | 1       |
| Klenk    | Nutmeg, powdered (spi... | 7325A130304  | 1       |
| Klenk    | Nutmeg, powdered (spi... | 7325A120903  | 2       |
| Klenk    | Oak bark, cut            | 761A110816   | 9       |
| Klenk    | Oak bark, cut            | 761A110816   | 2       |
| Klenk    | Oak bark, cut            | 761A110816   | 1       |
| Klenk    | Oak bark, cut            | C-280513-2   | 1       |
| Klenk    | Oak bark, cut            | 761A090420   | 2       |
| Klenk    | Olive leaf               | 2211B130425  | 3       |
| Klenk    | Olive leaf               | 2211B120417  | 2       |
| Klenk    | Olive leaf               | 2211B131025  | 1       |
| Klenk    | Olive leaf               | 2211B150818  | 1       |
| Klenk    | Orange peel, cut         | 531A130204   | 6       |
| Klenk    | Orange peel, cut         | 531a130204   | 1       |
| Klenk    | Orange peel, cut         | 531A091125   | 3       |
| Klenk    | Oregano herb             | 4221A120315  | 2       |

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| Supplier | Substance               | Batch          | Spectra |
|----------|-------------------------|----------------|---------|
| Klenk    | Orris root              | 6831B111013    | 1       |
| Klenk    | Orris root              | B130102        | 1       |
| Klenk    | Orris root              | B111013        | 1       |
| Klenk    | Parsley root, cut       | 6441A150811    | 1       |
| Klenk    | Parsley root, cut       | 6441A120110    | 1       |
| Klenk    | Parsley root, cut       | 6441A121024    | 5       |
| Klenk    | Parsley root, cut       | 6441A120606    | 7       |
| Klenk    | Parsley root, cut       | 6441A120283    | 1       |
| Klenk    | Parsley seed            | 7370A09120     | 1       |
| Klenk    | Parsley seed            | nachprüfung    | 1       |
| Klenk    | Passionflower herb, cut | A120329        | 2       |
| Klenk    | Passionflower herb, cut | 4231A-110913   | 1       |
| Klenk    | Passionflower herb, cut | 4231A120329    | 2       |
| Klenk    | Peony root, cut         | B110916        | 2       |
| Klenk    | Peony root, cut         | 6421B120327    | 1       |
| Klenk    | Peppermint leaf, cut    | 2181A110512    | 9       |
| Klenk    | Peppermint leaf, cut    | 2181A101013    | 10      |
| Klenk    | Peppermint leaf, cut    | 2181A100323    | 1       |
| Klenk    | Peppermint leaf, cut    | 1209211505     | 1       |
| Klenk    | Peppermint leaf, cut    | A130806        | 1       |
| Klenk    | Peppermint leaf, cut    | CH.2161B080818 | 1       |
| Klenk    | Peppermint leaf, cut    | A121009        | 1       |
| Klenk    | Peppermint leaf, cut    | 4113Q1505      | 1       |
| Klenk    | Peppermint leaf, cut    | 4513E1503      | 1       |
| Klenk    | Peppermint leaf, cut    | 2161A121206    | 15      |
| Klenk    | Peppermint leaf, cut    | 2181A130320    | 7       |
| Klenk    | Peppermint leaf, cut    | 2181B130717    | 10      |
| Klenk    | Peppermint leaf, cut    | 312172/3       | 1       |
| Klenk    | Peppermint leaf, cut    | 2161           | 1       |
| Klenk    | Peppermint leaf, cut    | 2161A130806    | 10      |
| Klenk    | Peppermint leaf, cut    | 2161A120718    | 4       |
| Klenk    | Peppermint leaf, cut    | 2161A121009    | 6       |
| Klenk    | Peppermint leaf, cut    | 2161A07020203  | 1       |
| Klenk    | Peppermint leaf, cut    | 2181A151119    | 1       |
| Klenk    | Peppermint leaf, cut    | 2161A110207    | 1       |
| Klenk    | Peppermint leaf, cut    | 2161A111207    | 1       |
| Klenk    | Peppermint leaf, cut    | 2161a121029    | 1       |
| Klenk    | Peppermint leaf, cut    | 2161A-121206   | 1       |
| Klenk    | Peppermint leaf, cut    | 2161B140321    | 1       |
| Klenk    | Peppermint leaf, cut    | 2183A120913    | 3       |
| Klenk    | Peppermint leaf, cut    | 1001311505     | 1       |
| Klenk    | Peppermint leaf, cut    | 2181A13020     | 1       |
| Klenk    | Peppermint leaf, cut    | 2181a120913    | 3       |
| Klenk    | Peppermint leaf, cut    | 2181A-120913   | 1       |
| Klenk    | Peppermint leaf, cut    | 2181A-101013   | 1       |
| Klenk    | Peppermint leaf, cut    | 2181A120913    | 39      |
| Klenk    | Peppermint leaf, cut    | 1913A-01505    | 1       |
| Klenk    | Primrose flower         | 1541B130808    | 6       |
| Klenk    | Primrose flower         | A111018        | 1       |
| Klenk    | Primrose flower         | B130808        | 1       |
| Klenk    | Primrose flower         | 1540A-100907   | 1       |
| Klenk    | Primrose flower         | 1541B100414    | 2       |
| Klenk    | Primrose flower         | B130808        | 1       |
| Klenk    | Primrose flower         | B110314        | 1       |
| Klenk    | Primrose flower         | 1541B110314    | 11      |
| Klenk    | Primrose flower         | 1540A100907    | 1       |
| Klenk    | Primrose root, cut      | 6461A100511    | 1       |
| Klenk    | Primrose root, cut      | B130218        | 3       |
| Klenk    | Psyllium seed           | 7380A120911    | 19      |
| Klenk    | Psyllium seed           | 7560A140203    | 1       |

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| Supplier | Substance             | Batch                | Spectra |
|----------|-----------------------|----------------------|---------|
| Klenk    | Psyllium seed         | 7380A120109          | 26      |
| Klenk    | Psyllium seed         | A120911              | 1       |
| Klenk    | Psyllium seed         | A130128              | 1       |
| Klenk    | Psyllium seed         | 7560A130418          | 1       |
| Klenk    | Psyllium seed         | A120109              | 1       |
| Klenk    | Psyllium seed         | 7560a120330          | 1       |
| Klenk    | Psyllium seed         | 7560A120330          | 1       |
| Klenk    | Psyllium seed         | 7380a120109          | 5       |
| Klenk    | Psyllium seed         | 7380a111018          | 1       |
| Klenk    | Psyllium seed         | 7380A111018          | 2       |
| Klenk    | Psyllium seed         | 7380A110317          | 1       |
| Klenk    | Psyllium seed         | 7380A150520          | 4       |
| Klenk    | Psyllium seed         | 7380A130128          | 6       |
| Klenk    | Raspberry leaf, cut   | 2291A121120          | 4       |
| Klenk    | Raspberry leaf, cut   | 2291A130320          | 1       |
| Klenk    | Raspberry leaf, cut   | 2271C120508          | 6       |
| Klenk    | Raspberry leaf, cut   | 2291A120813          | 1       |
| Klenk    | Raspberry leaf, cut   | 2291A110125          | 1       |
| Klenk    | Raspberry leaf, cut   | 2291A120806          | 6       |
| Klenk    | Raspberry leaf, cut   | 2291a111124          | 1       |
| Klenk    | Raspberry leaf, cut   | A130430              | 1       |
| Klenk    | Raspberry leaf, cut   | 12273107             | 1       |
| Klenk    | Red clover flower     | nachprüfung          | 3       |
| Klenk    | Red clover flower     | 7470A130311          | 1       |
| Klenk    | Red clover flower     | 1640A130122          | 16      |
| Klenk    | Red clover flower     | 1640A110727          | 3       |
| Klenk    | Red clover flower     | 811Q-07163           | 1       |
| Klenk    | Red clover flower     | 1640A120116          | 1       |
| Klenk    | Red clover flower     | 1640a130122          | 1       |
| Klenk    | Red-rose petal        | 1561A121016          | 1       |
| Klenk    | Red-rose petal, cut   | 1561B101210          | 3       |
| Klenk    | Red-rose petal, cut   | 1561A121016-34023101 | 1       |
| Klenk    | Red-rose petal, cut   | 1561A110404          | 1       |
| Klenk    | Redwood               | 5961B111219          | 1       |
| Klenk    | Restharrow root, cut  | 6411111110           | 1       |
| Klenk    | Restharrow root, cut  | 6411B111110          | 3       |
| Klenk    | Restharrow root, cut  | B111110              | 1       |
| Klenk    | Restharrow root, cut  | 6411B130404          | 4       |
| Klenk    | Restharrow root, cut  | 6411B101216          | 2       |
| Klenk    | Restharrow root, cut  | 4296345              | 1       |
| Klenk    | Rhubarb, cut          | 7761B130514          | 2       |
| Klenk    | Rhubarb, cut          | 6891B111118          | 1       |
| Klenk    | Ribwort plantain, cut | 4271A-110816         | 1       |
| Klenk    | Ribwort plantain, cut | 4271A130716          | 1       |
| Klenk    | Ribwort plantain, cut | 427A111125           | 1       |
| Klenk    | Ribwort plantain, cut | 4281N111121          | 2       |
| Klenk    | Ribwort plantain, cut | A110816              | 1       |
| Klenk    | Ribwort plantain, cut | 4271A100615          | 4       |
| Klenk    | Ribwort plantain, cut | 4271A110816          | 6       |
| Klenk    | Ribwort plantain, cut | 4271A130115          | 7       |
| Klenk    | Robert herb, cut      | 3951B121218          | 2       |
| Klenk    | Robert herb, cut      | 3951B12118           | 1       |
| Klenk    | Robert herb, cut      | 3951-A-110621        | 1       |
| Klenk    | Rose hips peel, cut   | 3613M-01543          | 1       |
| Klenk    | Rose hips peel, cut   | 2851A150310          | 4       |
| Klenk    | Rose hips peel, cut   | 2851A120102          | 5       |
| Klenk    | Rose hips peel, cut   | 2851A-110202         | 1       |
| Klenk    | Rose hips peel, cut   | 2851A120904          | 4       |
| Klenk    | Rose hips peel, cut   | 2851A110202          | 1       |
| Klenk    | Rose hips peel, cut   | 2851A101119          | 3       |

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| Supplier | Substance                | Batch         | Spectra |
|----------|--------------------------|---------------|---------|
| Klenk    | Rose hips peel, cut      | A120904       | 3       |
| Klenk    | Rose hips peel, cut      | 2841B111019   | 2       |
| Klenk    | Rose hips with peel, ... | 2841B081210   | 1       |
| Klenk    | Rose hips with peel, ... | A120719       | 1       |
| Klenk    | Rose hips with peel, ... | 3613M-01542   | 1       |
| Klenk    | Rose hips with peel, ... | B130523       | 1       |
| Klenk    | Rose hips with peel, ... | 2851A120904   | 1       |
| Klenk    | Rose hips with peel, ... | 2841B110317   | 1       |
| Klenk    | Rose hips with peel, ... | B111019       | 1       |
| Klenk    | Rose hips with peel, ... | A120904       | 1       |
| Klenk    | Roselle                  | 1431B-110519  | 1       |
| Klenk    | Roselle                  | 1431B130205   | 1       |
| Klenk    | Roselle                  | B130205       | 1       |
| Klenk    | Roselle                  | 1431B131015   | 2       |
| Klenk    | Roselle                  | 1431B111122   | 1       |
| Klenk    | Rosemary leaf, cut       | 2261a120224   | 4       |
| Klenk    | Rosemary leaf, cut       | 112E-01510    | 1       |
| Klenk    | Rosemary leaf, cut       | A130201       | 2       |
| Klenk    | Rosemary leaf, cut       |               | 1       |
| Klenk    | Rosemary leaf, cut       | 2261a130201   | 1       |
| Klenk    | Rosemary leaf, cut       | 2261A081117   | 1       |
| Klenk    | Rosemary leaf, cut       | 2261A100916   | 2       |
| Klenk    | Rosemary leaf, cut       | 2261A160905   | 1       |
| Klenk    | Rosemary leaf, cut       | 2261A150622   | 3       |
| Klenk    | Rosemary leaf, cut       | 2261A140910   | 3       |
| Klenk    | Rosemary leaf, cut       | 61A131118     | 1       |
| Klenk    | Rosemary leaf, cut       | 2261A120224   | 22      |
| Klenk    | Rosemary leaf, cut       | 2261A131118   | 10      |
| Klenk    | Rosemary leaf, cut       | 2261A130201   | 30      |
| Klenk    | Rosemary leaf, cut       | 2261a160329   | 1       |
| Klenk    | Rue herb, cut            | 4361A07020601 | 1       |
| Klenk    | Rue herb, cut            | A120207       | 1       |
| Klenk    | Rue herb, cut            | 4361A120207   | 1       |
| Klenk    | Rue herb, cut            | 4361A100707   | 3       |
| Klenk    | Saffron (spice)          | 384A110608    | 1       |
| Klenk    | Saffron (spice)          | 384A-120410   | 1       |
| Klenk    | Saffron (spice)          | 384a120410    | 1       |
| Klenk    | Saffron (spice)          | 384A130320    | 2       |
| Klenk    | Saffron filaments        | 380A130613    | 1       |
| Klenk    | Saffron filaments        | 380A120416    | 2       |
| Klenk    | Saffron filaments        | 380a120416    | 1       |
| Klenk    | Saffron filaments        | 380a130613    | 1       |
| Klenk    | Sage leaf, cut           | C120126       | 1       |
| Klenk    | Sage leaf, cut           | 2310A120403   | 1       |
| Klenk    | Sage leaf, cut           | 2301A110420   | 1       |
| Klenk    | Sage leaf, cut           | 2301C12126    | 1       |
| Klenk    | Sage leaf, cut           | 2301C120126   | 17      |
| Klenk    | Sage leaf, cut           | 2301C12026    | 1       |
| Klenk    | Sage leaf, cut           | 2301A100726   | 1       |
| Klenk    | Sage leaf, cut           | 2301c120126   | 2       |
| Klenk    | Sage leaf, cut           | 2301a120403   | 2       |
| Klenk    | Sage leaf, cut           | 21021313      | 1       |
| Klenk    | Sarsaparilla root, cut   | 6561B111108   | 2       |
| Klenk    | Sarsaparilla root, cut   | B111108       | 1       |
| Klenk    | Senna leaf, cut          | B130214       | 1       |
| Klenk    | Senna leaf, cut          | 2331B150903   | 1       |
| Klenk    | Senna leaf, cut          | 2331C130326   | 14      |
| Klenk    | Senna leaf, cut          | 2331B120521   | 6       |
| Klenk    | Senna leaf, cut          | 2331B110907   | 2       |
| Klenk    | Senna leaf, cut          | 2331B120403   | 5       |

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| Supplier | Substance                | Batch          | Spectra |
|----------|--------------------------|----------------|---------|
| Klenk    | Senna leaf, cut          | 2331c130326    | 2       |
| Klenk    | Senna leaf, cut          | 2331b130214    | 1       |
| Klenk    | Senna leaf, cut          | 2331B130214    | 4       |
| Klenk    | Senna leaf, cut          | 2331C120614    | 12      |
| Klenk    | Senna leaf, cut          | 2331A100525    | 2       |
| Klenk    | Senna leaf, cut          | 2331A110207    | 2       |
| Klenk    | Senna pods, tinnevelly   | 1041B120327    | 2       |
| Klenk    | Shepherd's purse, cut    | 3671B111201    | 1       |
| Klenk    | Shepherd's purse, cut    | 3671A-100414   | 2       |
| Klenk    | Shepherd's purse, cut    | B111201        | 1       |
| Klenk    | Silverweed, cut          | 3551A130903    | 1       |
| Klenk    | Silverweed, cut          | A110913        | 2       |
| Klenk    | Silverweed, cut          | 3551A110913    | 2       |
| Klenk    | Silverweed, cut          | H-280513-3     | 1       |
| Klenk    | Sodium dihydrogen pho... | 1301005-01     | 1       |
| Klenk    | Sodium hydrogen carbo... | 12d11-n02      | 1       |
| Klenk    | Sorrel herb, cut         | 11165306       | 1       |
| Klenk    | Spearmint leaf, cut      | 2171A120711    | 1       |
| Klenk    | St. John's wort, cut     | 4021A100819    | 28      |
| Klenk    | St. John's wort, cut     | 4021B110321    | 4       |
| Klenk    | St. John's wort, cut     | 15068103       | 2       |
| Klenk    | St. John's wort, cut     | 268913         | 2       |
| Klenk    | St. John's wort, cut     | 4021A100919    | 1       |
| Klenk    | St. John's wort, cut     | 4021A00819     | 1       |
| Klenk    | St. John's wort, cut     | 4021a120604    | 2       |
| Klenk    | St. John's wort, cut     | 4021A130612    | 5       |
| Klenk    | St. John's wort, cut     | A121120        | 1       |
| Klenk    | St. John's wort, cut     | A130612        | 3       |
| Klenk    | St. John's wort, cut     | 4021a100819    | 1       |
| Klenk    | St. John's wort, cut     | 4021A100819914 | 2       |
| Klenk    | St. John's wort, cut     | 4021A120905    | 10      |
| Klenk    | Star anise               | 2690A111013    | 3       |
| Klenk    | Star anise               | 2690A120809    | 1       |
| Klenk    | Star anise               | 2696B111109    | 1       |
| Klenk    | Star anise               | B111109        | 1       |
| Klenk    | Star anise               | 2690A130903    | 2       |
| Klenk    | Star anise               | 2690A101026    | 2       |
| Klenk    | Star anise               | 2695B120308    | 1       |
| Klenk    | Stemless carline root    | 69191B120726   | 1       |
| Klenk    | Stemless carline root    | 6191b120726    | 3       |
| Klenk    | Stemless carline root    | 6191B130228    | 2       |
| Klenk    | Stemless carline root    | 6191B120726    | 5       |
| Klenk    | Stemless carline root    | B110831        | 1       |
| Klenk    | Stemless carline root    | 6194b110831    | 1       |
| Klenk    | Stemless carline root    | 6194B110831    | 1       |
| Klenk    | Stemless carline root    | 12097301       | 1       |
| Klenk    | Strawberry leaf, cut     | 2031B110224    | 2       |
| Klenk    | Strawberry leaf, cut     | 2031A130430    | 2       |
| Klenk    | Strawberry leaf, cut     | B120925        | 1       |
| Klenk    | Strawberry leaf, cut     | A130430        | 1       |
| Klenk    | Sunflower, cut           | 1701B091013    | 1       |
| Klenk    | Sunflower, cut           | 1711I-07036    | 1       |
| Klenk    | Sweet fennel             | 2870A130304    | 4       |
| Klenk    | Sweet fennel             | 2870130304A    | 1       |
| Klenk    | Sweet fennel             | 2870A140528    | 1       |
| Klenk    | Sweet fennel             | 2870A131002    | 1       |
| Klenk    | Sweet woodruff herb, ... | 3601B140321    | 1       |
| Klenk    | Sweet woodruff herb, ... | B090114        | 3       |
| Klenk    | Sweet woodruff herb, ... | 3601B090114    | 1       |
| Klenk    | Tall golden rod, cut     | 4521A100414    | 1       |

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| Supplier | Substance               | Batch        | Spectra |
|----------|-------------------------|--------------|---------|
| Klenk    | Tall golden rod, cut    | 1781B110706  | 1       |
| Klenk    | Tall golden rod, cut    | A110209      | 1       |
| Klenk    | Tall golden rod, cut    | 4521A110209  | 5       |
| Klenk    | Tall golden rod, cut    | 4521A-110816 | 1       |
| Klenk    | Tall hawkweed, cut      | 3611B11105   | 1       |
| Klenk    | Tall hawkweed, cut      | B111005      | 1       |
| Klenk    | Theriac, powdered       | 12189403     | 1       |
| Klenk    | Thyme, rubbed           | 4622A130910  | 2       |
| Klenk    | Thyme, rubbed           | 4622a130109  | 4       |
| Klenk    | Thyme, rubbed           | 4622B110519  | 3       |
| Klenk    | Thyme, rubbed           | 1005         | 1       |
| Klenk    | Thyme, rubbed           | 1910211688   | 1       |
| Klenk    | Thyme, rubbed           | 11121307     | 1       |
| Klenk    | Thyme, rubbed           | A130910      | 3       |
| Klenk    | Thyme, rubbed           | 4622A-120111 | 1       |
| Klenk    | Thyme, rubbed           | 2902211688   | 1       |
| Klenk    | Thyme, rubbed           | 4622a110728  | 2       |
| Klenk    | Thyme, rubbed           | 4622A1200111 | 1       |
| Klenk    | Thyme, rubbed           | 4622A141203  | 1       |
| Klenk    | Thyme, rubbed           | 2103311688   | 1       |
| Klenk    | Thyme, rubbed           | 4622A130109  | 85      |
| Klenk    | Thyme, rubbed           | 4622a120111  | 4       |
| Klenk    | Tormentil               | 6914b120112  | 1       |
| Klenk    | Tormentil               | 6911B150825  | 1       |
| Klenk    | Tormentil               | 6911B111013  | 11      |
| Klenk    | Tormentil               | 6911B141114  | 1       |
| Klenk    | Tormentil               | 6911B131029  | 4       |
| Klenk    | Tormentil               | 6911B140227  | 1       |
| Klenk    | Trichloroacetic acid    | 11294318     | 2       |
| Klenk    | Turmeric root, cut      | 6741a110202  | 1       |
| Klenk    | Turmeric root, cut      | 6741B121030  | 1       |
| Klenk    | Turmeric, javanese, cut | 6731B150630  | 1       |
| Klenk    | Turmeric, javanese, cut | B130117      | 1       |
| Klenk    | Valerian root, cut      | 6641B130226  | 11      |
| Klenk    | Valerian root, cut      | 6641B100823  | 1       |
| Klenk    | Valerian root, cut      | 6641B-110317 | 1       |
| Klenk    | Valerian root, cut      | 6641B120417  | 3       |
| Klenk    | Valerian root, cut      | 6645B130226  | 1       |
| Klenk    | Valerian root, cut      | 13196808     | 3       |
| Klenk    | Verbena herb, cut       | 4654B120611  | 1       |
| Klenk    | Verbena herb, cut       | 4651B130611  | 2       |
| Klenk    | Verbena herb, cut       | 4651B110310  | 3       |
| Klenk    | Verbena herb, cut       | 4651B120611  | 18      |
| Klenk    | Verbena herb, cut       | 12345        | 1       |
| Klenk    | Verbena herb, cut       | A130923      | 1       |
| Klenk    | Verbena herb, cut       | 4651A070828  | 3       |
| Klenk    | Vine leaf, cut          | 2491B120918  | 1       |
| Klenk    | Vine leaf, cut          | 2491B100707  | 1       |
| Klenk    | Walnut bark, cut        | 711B111020   | 6       |
| Klenk    | Walnut bark, cut        | 711b120613   | 1       |
| Klenk    | Walnut bark, cut        | 7114B120906  | 1       |
| Klenk    | Walnut bark, cut        | 711B080806   | 1       |
| Klenk    | Walnut bark, cut        | 711B120906   | 2       |
| Klenk    | Walnut bark, cut        | 711B120613   | 3       |
| Klenk    | Walnut leaf, cut        | 2111A110816  | 1       |
| Klenk    | Walnut leaf, cut        | 2111A130410  | 4       |
| Klenk    | Walnut leaf, cut        | A130410      | 1       |
| Klenk    | Walnut leaf, cut        | 2111A131029  | 1       |
| Klenk    | Walnut leaf, cut        | 2111A-120123 | 1       |
| Klenk    | Walnut leaf, cut        | F-280513-1   | 1       |

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| Supplier        | Substance                | Batch        | Spectra |
|-----------------|--------------------------|--------------|---------|
| Klenk           | White deadnettle flower  | 1470A120111  | 7       |
| Klenk           | White deadnettle flower  | 1470a080103  | 1       |
| Klenk           | White deadnettle flower  | nachprüfung  | 1       |
| Klenk           | White deadnettle flower  | 1470A080910  | 1       |
| Klenk           | White deadnettle flower  | 1470A080103  | 1       |
| Klenk           | White deadnettle flower  | 1470a120111  | 1       |
| Klenk           | White mustard seed, p... | 7254A141202  | 1       |
| Klenk           | Wild pansy, cut          | B130715      | 1       |
| Klenk           | Wild pansy, cut          | 11216103     | 5       |
| Klenk           | Wild pansy, cut          | 4681A120806  | 15      |
| Klenk           | Wild pansy, cut          | 4681A110303  | 5       |
| Klenk           | Wild pansy, cut          | 4681A-120806 | 1       |
| Klenk           | Wild pansy, cut          | 4681B130715  | 7       |
| Klenk           | Willow bark, cut         | 811B100910   | 4       |
| Klenk           | Willowherb, small flo... | 4721A120418  | 10      |
| Klenk           | Willowherb, small flo... | 4721B130528  | 1       |
| Klenk           | Willowherb, small flo... | 4721A101010  | 4       |
| Klenk           | Willowherb, small flo... | 2512U-01641  | 1       |
| Klenk           | Willowherb, small flo... | 4721C2120321 | 2       |
| Klenk           | Willowherb, small flo... | 4721C130618  | 4       |
| Klenk           | Willowherb, small flo... | A120418      | 1       |
| Klenk           | Willowherb, small flo... | C120321      | 1       |
| Klenk           | Willowherb, small flo... | 4721A120903  | 7       |
| Klenk           | Willowherb, small flo... | 4721C110701  | 4       |
| Klenk           | Wormwood herb, cut       | 3461A1100324 | 1       |
| Klenk           | Wormwood herb, cut       | 3461A110324  | 2       |
| Klenk           | Wormwood herb, cut       | 3461A121130  | 2       |
| Klenk           | Wormwood herb, cut       | A110324      | 1       |
| Klenk           | Yarrow flower, rubbed    | A110816      | 3       |
| Klenk           | Yarrow flower, rubbed    | 1511A111129  | 1       |
| Klenk           | Yarrow flower, rubbed    | 4181A121130  | 1       |
| Klenk           | Yarrow herb, cut         | 15333007     | 1       |
| Klenk           | Yarrow herb, cut         | 4181A101102  | 3       |
| Klenk           | Yarrow herb, cut         | 4181A130710  | 1       |
| Klenk           | Yarrow herb, cut         | 4181A110111  | 19      |
| Klenk           | Yarrow herb, cut         | 4181130709   | 1       |
| Klenk           | Yarrow herb, cut         | 4181a11011   | 1       |
| Klenk           | Yarrow herb, cut         | 4181B130709  | 2       |
| Klenk           | Yarrow herb, cut         | 4181A111122  | 7       |
| Klenk           | Yarrow herb, cut         | 4181A121130  | 16      |
| Klenk           | Yarrow herb, cut         | A130709      | 1       |
| Klenk           | Yarrow herb, cut         | 4181a130513  | 1       |
| Klenk           | Yarrow herb, cut         | 4181A130513  | 12      |
| Klenk           | Yellow chaste weed, cut  | 1591A110511  | 14      |
| Klenk           | Yellow chaste weed, cut  | 1591A-110511 | 1       |
| Klenk           | Zedoary root, cut        | 6941B121025  | 2       |
| Klenk           | Zedoary root, cut        | 6941B110329  | 2       |
| Klenk           | Zedoary root, powdered   | 12007505     | 1       |
| Koisser         | Glucosamine sulfate 2... | 120719K371   | 1       |
| Kräuter Sc      | Betony herb, cut         | 38546        | 1       |
| kräuter schulte | Bitter orange peel, cut  | 51265        | 1       |
| kräuter schulte | Gentian root, cut        | 52348        | 1       |
| kräuter schulte | Red-rose petal, cut      | 47543        | 1       |
| kräuter schulte | Tormentil                | 51952        | 1       |
| Kräuter Schulte | Abrotani herb, cut       | 50870        | 1       |
| Kräuter Schulte | Black cohosh, cut        | 3308M-02176  | 1       |
| Kräuter Schulte | Blackthorn flower, ru... | 53233        | 2       |
| Kräuter Schulte | Bucho leaf               | 54519        | 1       |
| Kräuter Schulte | China Pai Mu Tan         | 52783        | 1       |
| Kräuter Schulte | Couch grass rhizome, ... | 53016        | 2       |

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| Supplier                 | Substance                | Batch          | Spectra |
|--------------------------|--------------------------|----------------|---------|
| Kräuter Schulte          | Dill fruit               | 6363           | 1       |
| Kräuter Schulte          | Dryas octopetala herb... | 38970          | 1       |
| Kräuter Schulte          | Geum urbanum herb, cut   | 51737          | 1       |
| Kräuter Schulte          | Meadowsweet flower, r... | 53473          | 1       |
| Kräuter Schulte          | Meadowsweet flower, r... | 51369          | 1       |
| Kräuter Schulte          | Red clover flower        | 53778          | 1       |
| Kräuter Schulte          | Red tea                  | 52029          | 1       |
| Kräuter Schulte          | Saponaria root, cut      | 54500          | 1       |
| Kräuter Schulte          | Saponaria root, cut      | 54524          | 2       |
| Kräuter Schulte          | Saponaria root, cut      | 54977          | 1       |
| Kräuter-Schulte          | Peppermint leaf, cut     | 56254          | 1       |
| Kräuter-Schulte          | Sorrel herb, cut         | 55272          | 1       |
| Kräuter-Schulte          | Sweet woodruff herb, ... | 52878          | 1       |
| Kräuter-Schulte          | Zedoary root, cut        | 25713          | 1       |
| linnea/salficalcan       | Griffonia seed extract   | 50814001       | 1       |
| Lohman                   | Sodium sulfate decahy... | 1210005-02     | 3       |
| Lycored                  | Caromix                  | CMXVBAF-011301 | 1       |
| Macfarlan Smith/Noweda   | Cocaine hydrochloride    | 15224802       | 1       |
| Macsen laboratories/P... | Methylrosanilinium ch... | 1989           | 1       |
| Magnesia/ Noweda         | Magnesium sulfate hep... | 26251          | 3       |
| meltem                   | Sweet fennel             | türkei         | 1       |
| Merck                    | Codeine phosphate hem... | 120765         | 1       |
| Merck                    | Heavy alkaline bismut... | 75419201       | 1       |
| Merck                    | Trichloroacetic acid     | 12821          | 1       |
| Microsin Pharmorgana     | Copper orotate dihydr... | 565313         | 1       |
| Microsin Pharmorgana     | Zinc orotate dihydrate   | 0RZ00113       | 1       |
| Nachprüfung              | Abrotani herb, cut       | 3451A070919    | 1       |
| Nachprüfung              | Aniseed                  | 5010U-01530    | 1       |
| Nachprüfung              | Black cohosh, cut        | 10281113       | 1       |
| Nachprüfung              | Blackcurrant leaf, cut   | 1003           | 1       |
| Nachprüfung              | Fenugreek, powdered      | 2412E02239     | 1       |
| Nachprüfung              | Hay flower               | 1911E01459     | 1       |
| Nachprüfung              | Heather, cut             | 5110A03224     | 1       |
| Nachprüfung              | Potassium hydrocarbon... | 1105           | 1       |
| Nachprüfung              | Stemless carline root    | 2812U02133     | 1       |
| Nachprüfung              | Wild pansy, cut          | 10291007       | 1       |
| noweda                   | Aniseed                  | 11101201       | 3       |
| noweda                   | Dandelion root, cut      |                | 1       |
| noweda                   | Iceland moss, cut        |                | 1       |
| noweda                   | Lavender flower          | 11327904       | 1       |
| noweda                   | Nettle leaf, cut         | 10291404       | 1       |
| noweda                   | Valerian root, cut       | 11103603       | 1       |
| noweda                   | Walnut leaf, cut         |                | 1       |
| noweda                   | Wormwood herb, cut       | 11085709       | 1       |
| Noweda                   | Agnus castus fruit       | 12016902       | 2       |
| Noweda                   | Agrimony, cut            | 9300106        | 1       |
| Noweda                   | Alchemilla, cut          | 1215301        | 1       |
| Noweda                   | Aloes, cape, powdered    | 11132104       | 1       |
| Noweda                   | Ammonium hydrogen car... | 11145601       | 3       |
| Noweda                   | Angelica root            | 38011111       | 2       |
| Noweda                   | Angelica root            | 272720         | 2       |
| Noweda                   | Angelica root            | 12070802       | 1       |
| Noweda                   | Aniseed                  | 11101203       | 10      |
| Noweda                   | Aniseed                  | 521103501      | 1       |
| Noweda                   | Bean shells, cut         | 265670         | 1       |
| Noweda                   | Bearberry leaf, cut      | 267926         | 2       |
| Noweda                   | Bearberry leaf, cut      | 11213011       | 6       |
| Noweda                   | Bentonite                | 11304415       | 1       |
| Noweda                   | Bentonite                | 1301012-01     | 1       |
| Noweda                   | Birch leaf, cut          | 11189508       | 2       |

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| <b>Supplier</b> | <b>Substance</b>         | <b>Batch</b>  | <b>Spectra</b> |
|-----------------|--------------------------|---------------|----------------|
| Noweda          | Birch leaf, cut          | 12193004      | 7              |
| Noweda          | Birch leaf, cut          | 12193105      | 4              |
| Noweda          | Bitter fennel            | 12094707      | 1              |
| Noweda          | Bitter orange flower ... | 11049211      | 1              |
| Noweda          | Black mustard seed, p... | 12350204      | 7              |
| Noweda          | Boldo leaf, cut          | 11016507      | 1              |
| Noweda          | Caffeine citrate         | CCC-1101      | 1              |
| Noweda          | Calcium hydrogen phos... | 11287501      | 2              |
| Noweda          | Calendula flower, cut    | 12221709      | 9              |
| Noweda          | Calendula flower, cut    | 268876        | 1              |
| Noweda          | Caraway fruit            | 12226503      | 6              |
| Noweda          | Caraway fruit, pounded   | 12116904      | 3              |
| Noweda          | Centaury, cut            | 10104012      | 2              |
| Noweda          | Copper (II) sulfate p... | 12B09-N10     | 1              |
| Noweda          | Copper (II) sulfate p... | 11F21-N03     | 1              |
| Noweda          | Coriander                | 13010302      | 4              |
| Noweda          | Coriander                | 12080902      | 1              |
| Noweda          | Damiana leaf, cut        | 200151        | 1              |
| Noweda          | Dandelion herb with r... | 521101126     | 1              |
| Noweda          | Dandelion herb with r... | 11217101      | 1              |
| Noweda          | Dandelion herb with r... | 11030311      | 5              |
| Noweda          | Dandelion herb with r... | 11030305      | 3              |
| Noweda          | Dithranole               | DT/375/2012D  | 3              |
| Noweda          | Dithranole               | APDT/375/2012 | 2              |
| Noweda          | Elecampane rhizome, cut  | 6341B111118   | 3              |
| Noweda          | Equisetum stem, cut      | 10375511      | 1              |
| Noweda          | Hawthorn leaf with fl... | 11366001      | 2              |
| Noweda          | Hawthorn leaf with fl... | 10273515      | 7              |
| Noweda          | Heavy alkaline bismut... | 13/01-N02     | 1              |
| Noweda          | Hop strobile             | 274725        | 1              |
| Noweda          | Hop strobile             | 12008313      | 1              |
| Noweda          | Horse chestnut leaf, ... | 11063502      | 2              |
| Noweda          | Horse chestnut leaf, ... | 11063501      | 1              |
| Noweda          | Iceland moss, cut        | 11101602      | 1              |
| Noweda          | Ispaghula seed           | 7560A110125   | 1              |
| Noweda          | Java tea, cut            | 2221B101213   | 2              |
| Noweda          | Juniper                  | 521101635     | 1              |
| Noweda          | Ladys bedstraw herb, ... | 10375701      | 1              |
| Noweda          | Laurel leaf              | 12299101      | 2              |
| Noweda          | Lime flower, cut         | 10273608      | 3              |
| Noweda          | Lime flower, cut         | 12170702      | 4              |
| Noweda          | Liquorice root, peeled   | 521200852     | 1              |
| Noweda          | Liquorice root, peeled   | 70226/1       | 1              |
| Noweda          | Lycopodium herb, cut     | 9378808       | 1              |
| Noweda          | Lycopodium herb, cut     | 11050001      | 1              |
| Noweda          | Magnesium chloride he... | 11H01-N03     | 1              |
| Noweda          | Magnesium sulfate hep... | 11H29-N02     | 3              |
| Noweda          | Manna, cut               | 5221A110817   | 2              |
| Noweda          | Manna, powdered          | 11170102      | 1              |
| Noweda          | Marian thistle herb, ... | 10315905      | 1              |
| Noweda          | Marrubium vulgare her... | 4141A080513   | 1              |
| Noweda          | Marshmallow leaf, cut    | 13199604      | 5              |
| Noweda          | Matricaria flower        | 12111903      | 3              |
| Noweda          | Matricaria flower        | 11169603      | 2              |
| Noweda          | Melissa leaf, cut        | 10310913      | 1              |
| Noweda          | Methylrosanilinium ch... | 9238104       | 1              |
| Noweda          | Methylrosanilinium ch... | 12H28-N06     | 1              |
| Noweda          | Methylrosanilinium ch... | 2159          | 2              |
| Noweda          | Methylrosanilinium ch... | 9238101       | 1              |
| Noweda          | Molecular distilled g... | 11160010      | 1              |

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| Supplier                  | Substance                | Batch        | Spectra |
|---------------------------|--------------------------|--------------|---------|
| Noweda                    | Nettle leaf, cut         | 41010712     | 1       |
| Noweda                    | Nettle leaf, cut         | 262338       | 1       |
| Noweda                    | Nettle leaf, cut         | 10375901     | 5       |
| Noweda                    | Nystatin                 | 1207009-01   | 10      |
| Noweda                    | Oak bark, cut            | 10348617     | 11      |
| Noweda                    | Oat straw, cut           | 11280003     | 1       |
| Noweda                    | Parsley seed             | 7370A091120  | 5       |
| Noweda                    | Passionflower herb, cut  | 10079510     | 1       |
| Noweda                    | Peppermint leaf, cut     | 2911U-01505  | 1       |
| Noweda                    | Peppermint leaf, cut     | 11294411     | 2       |
| Noweda                    | Potassium hydrocarbon... | 1004019-01   | 1       |
| Noweda                    | Prednisolone 1:10 (ri... | 11L13-N06    | 1       |
| Noweda                    | Primrose root, cut       | 12064504     | 7       |
| Noweda                    | Raspberry leaf, cut      | 12103101     | 11      |
| Noweda                    | Restharrow root, cut     | 272831       | 3       |
| Noweda                    | Restharrow root, cut     | 11103102     | 1       |
| Noweda                    | Rhubarb, cut             | 6891B100421  | 1       |
| Noweda                    | Ribwort plantain, cut    | 10315712     | 4       |
| Noweda                    | Ribwort plantain, cut    | 251029       | 1       |
| Noweda                    | Rose hips peel, cut      | 275394       | 3       |
| Noweda                    | Roselle                  | 11036507     | 2       |
| Noweda                    | Sage leaf, cut           | 11056119     | 2       |
| Noweda                    | Sage leaf, cut           | 11347511     | 12      |
| Noweda                    | Senna leaf, cut          | 11277305     | 2       |
| Noweda                    | Shepherd's purse, cut    | 11036409     | 1       |
| Noweda                    | Sodium hydrogen carbo... | 11197801     | 1       |
| Noweda                    | Stemless carline root    | 12163702     | 3       |
| Noweda                    | Stemless carline root    | 11198101     | 1       |
| Noweda                    | Tall golden rod, cut     | 11280306     | 4       |
| Noweda                    | Theriac, powdered        | 11082404     | 1       |
| Noweda                    | Thyme, rubbed            | 11345014     | 18      |
| Noweda                    | Thyme, rubbed            | 11345007     | 7       |
| Noweda                    | Thyme, rubbed            | 11345002     | 4       |
| Noweda                    | Thyme, rubbed            | 521303908    | 1       |
| Noweda                    | Tonka beans              | 1040A111026  | 1       |
| Noweda                    | Tragacanth, powdered     | 11128910     | 1       |
| Noweda                    | Tragacanth, powdered     | 12108807     | 1       |
| Noweda                    | Valerian root, cut       | 11103609     | 6       |
| Noweda                    | Valerian root, cut       | 12033804     | 10      |
| Noweda                    | Walnut leaf, cut         | 10050414     | 1       |
| Noweda                    | Walnut leaf, cut         | 10050416     | 2       |
| Noweda                    | Willow bark, cut         | 4609A-01305  | 1       |
| Noweda                    | Willowherb, small flo... | 10326106     | 3       |
| Noweda                    | Yarrow herb, cut         | 12378603     | 1       |
| Noweda                    | Zedoary root, cut        | 11091605     | 5       |
| Noweda 06.04.2016         | Bitter fennel            | 15443201     | 1       |
| Noweda/Henry Lamotte      | Black mustard seed, p... | 1493708      | 1       |
| Noweda10.02.2017          | Tormentil                | 15364313     | 1       |
| Otto Fischer GmbH         | Sodium hydrogen carbo... | 6521021      | 1       |
| Phagron/Ph                | Aluminium chloride he... | 11I23-N06    | 1       |
| Pharmachem.Pöckneck/Ph... | Amphetamine sulfate      | 13G08-N11    | 4       |
| Pharmorgana               | Caromix                  | cmx-PL101112 | 1       |
| Pharmorgana               | Copper orotate dihydr... | CH-565313    | 1       |
| Phoenix                   | Aluminium chloride he... | 13D22-N09    | 37      |
| Phoenix                   | Aluminium chloride he... | 11/23-N06    | 4       |
| Phoenix                   | Elder flower, rubbed     | 10291309     | 3       |
| Phoenix                   | Fenugreek                | 11313206     | 7       |
| Phoenix                   | Gentian root, cut        | 6311B120104  | 1       |
| Phoenix                   | Juniper                  |              | 1       |
| Phoenix                   | Magnesium sulfate hep... | 12L10-N07    | 14      |

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| Supplier              | Substance                | Batch        | Spectra |
|-----------------------|--------------------------|--------------|---------|
| Phoenix               | Manna, cut               | 522A120509   | 1       |
| Phoenix               | Methadone hydrochloride  | 15244715     | 1       |
| Phoenix               | Potassium hydrocarbon... | 12141915     | 5       |
| Phoenix               | Raspberry leaf, cut      | 10136409     | 1       |
| Phoenix               | Ribwort plantain, cut    | 4271A11016   | 1       |
| Phoenix               | Sage leaf, cut           | 231C130326   | 1       |
| Phoenix               | Sodium hydrogen carbo... | 13B18-N03    | 1       |
| Phoenix               | Tall golden rod, cut     | 265283       | 2       |
| Phoenix               | Zedoary root, cut        | 13010104     | 2       |
| PHOENIX 19.05.2014    | Black pepper             | 13221105     | 1       |
| Phoenix 27.03.2012    | Linseed                  | 11177302     | 1       |
| Phoenix am 03.12.2010 | Bearberry leaf, cut      | 4910B-1518   | 1       |
| PHOENIX am 08.06.2012 | Common wormwood herb,... | 12016703     | 1       |
| Phoenix am 11.06.2012 | Sage leaf, cut           | 2301A110204  | 11      |
| PHOENIX am 14.05.2012 | Artichoke leaf, cut      | 11151905     | 1       |
| Phoenix am 30.01.2013 | Matricaria flower        | 1290A        | 1       |
| Phoenix, 04.09.2012   | Nettle leaf, cut         | 12195002     | 4       |
| Phoenix, 13.09.2012   | Thyme, rubbed            | 44622A120111 | 1       |
| Phonix                | Linseed                  | 13296703     | 3       |
| Phönix                | Aluminium chloride he... | 12/27-N01    | 8       |
| Phönix                | Aluminium potassium s... | 14263801     | 1       |
| Phönix                | Aluminium potassium s... | 110804902    | 1       |
| Phönix                | Amphetamine sulfate      | 13B11N04     | 1       |
| Phönix                | Birch leaf, cut          | 1901120802   | 1       |
| Phönix                | Centaury, cut            | 11093612     | 2       |
| Phönix                | Cinnamon rods (Ceylon... | 610A130927   | 1       |
| Phönix                | Coltsfoot leaf, cut      | 278296       | 3       |
| Phönix                | Common broom herb, cut   | 12358801     | 2       |
| Phönix                | Creatine                 | mysjhskeu    | 1       |
| Phönix                | Dandelion herb with r... | 6611B110131  | 2       |
| Phönix                | Equisetum stem, cut      | 12288807     | 2       |
| Phönix                | Gentian root, cut        | 6311B120315  | 8       |
| Phönix                | Gentian root, cut        | 269197       | 3       |
| Phönix                | Ginger, peeled           | 13310601     | 1       |
| Phönix                | Hyssop herb, cut         | 11374306     | 1       |
| Phönix                | Ivy leaf, cut            | 11101102     | 1       |
| Phönix                | Jasmine flower           | 12143206     | 1       |
| Phönix                | Java tea, cut            | 12225701     | 1       |
| Phönix                | Juniper                  | 13020903     | 1       |
| Phönix                | Lime flower, cut         | 1611A12120   | 1       |
| Phönix                | Linseed                  | 7307A111107  | 13      |
| Phönix                | Liquorice root, natur... | 276425       | 1       |
| Phönix                | Male speedwell wort, ... | 13089201     | 4       |
| Phönix                | Marshmallow root, pee... | 6071A130612  | 4       |
| Phönix                | Marshmallow root, pee... | 6071a120314  | 1       |
| Phönix                | Matricaria flower        | 1300A120426  | 1       |
| Phönix                | Melilot herb, cut        | 1237903      | 1       |
| Phönix                | Melissa leaf, cut        | 2161A150324  | 1       |
| Phönix                | Nystatin                 | 12017005     | 3       |
| Phönix                | Oak bark, cut            | 10348609     | 3       |
| Phönix                | Peppermint leaf, cut     | 2181A141016  | 1       |
| Phönix                | Rhubarb, cut             | 12211905     | 5       |
| Phönix                | Rose hips with peel, ... | 2841B130523  | 1       |
| Phönix                | Rose hips with peel, ... | 10281021     | 1       |
| Phönix                | Rose hips with peel, ... | 2841B130523  | 1       |
| Phönix                | Silverweed, cut          | 11328107     | 7       |
| Phönix                | Sodium carbonate deca... | 13036904     | 3       |
| Phönix                | Sodium hydrogen carbo... | 206027       | 2       |
| Phönix                | Sodium hydrogen carbo... | 13390515     | 1       |
| Phönix                | Sodium monohydrogenph... | 1302800,     | 1       |

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| Supplier           | Substance                | Batch            | Spectra |
|--------------------|--------------------------|------------------|---------|
| Phönix             | Sodium monohydrogenph... | 13028101         | 1       |
| Phönix             | Talcum                   | 10148805Retest   | 1       |
| Phönix             | Wormwood herb, cut       | 12355806         | 6       |
| Phönix             | Yarrow herb, cut         | 1237962          | 1       |
| Phönix             | Yarrow herb, cut         | 13029103         | 18      |
| Phönix             | Aluminium potassium s... | 13356108         | 1       |
| Phönix 04.03.13    | Saponaria root, cut      | 6561B111108      | 1       |
| Phönix 05.10.2012  | Calendula flower, cut    | 121005           | 1       |
| Phönix 05.10.2012  | Walnut leaf, cut         | 121005           | 1       |
| Phönix 05.10.2012  | Yarrow herb, cut         | 121005           | 1       |
| Phönix 08.03.13    | Solanum dulcamara ste... | 5601A080513      | 4       |
| Phönix 08.08.2012  | Caraway fruit            | 1103213          | 1       |
| Phönix 10.01.2014  | Senna leaf, cut          | 13136707         | 1       |
| Phönix 12.10.13    | Knotgrass, cut           | 12368906         | 4       |
| Phönix 18.10.2013  | Sodium dihydrogen pho... | 12198512         | 1       |
| phönix 22.01.2013  | Yarrow herb, cut         | 271873           | 1       |
| Phönix 23.08.2012  | Bearberry leaf, cut      | 23910B120314     | 1       |
| Phönix 24.09.2012  | Mistletoe, cut           | 120924           | 1       |
| Phönix 24.12.12    | Valerian root, cut       |                  | 1       |
| Phönix 27.03.2013  | Calcium chloride dihy... | 1107010-02       | 1       |
| Phönix 31.10.12    | Passionflower herb, cut  | 12031701         | 2       |
| phönix 8.08.2013   | Juniper                  | 289017           | 1       |
| Phönix Gotha       | Goat's rue, cut          | 11307905         | 1       |
| Phönix Gotha       | Marjoram herb, rubbed    | 11212709         | 1       |
| Phönix Gotha       | Nystatin                 | 4014941          | 1       |
| Phönix Gotha       | Sodium monohydrogenph... |                  | 1       |
| Phönix Gotha       | Sodium thiosulfate pe... | 10E07-N13        | 1       |
| Phönix Gotha       | Stemless carline root    | 6191B111205      | 1       |
| phönix, 13.06.2012 | Calcium chloride dihy... | 11230918         | 1       |
| phönix, 14.01.2013 | Hop strobile             | 130114           | 1       |
| Phönix, 15.01.2013 | Aluminium potassium s... | 12I24-M03        | 1       |
| Phönix/            | Alchemilla, cut          | 14066009         | 2       |
| Phönix/            | St. John's wort, cut     | 14065707         | 1       |
| Phönix/Euro        | Magnesium chloride he... | 1208025-01       | 2       |
| Phönix/Phönix      | Black mustard seed, p... | 16333503         | 1       |
| Probe              | Elder root, cut          | 12345            | 1       |
| Probe              | Peppermint leaf, cut     | 1223456          | 1       |
| Productos Quimicos | D-(+)-mannose            | 16000524         | 1       |
| Purren Apotheke    | Heavy alkaline bismut... | 11H31-N06        | 1       |
| Redwood            | Damiana leaf, cut        | 216451           | 1       |
| Richter            | Common wormwood herb,... | b200112          | 1       |
| Richter            | Elecampane rhizome, cut  | P158683          | 1       |
| Richter            | Gentian root, cut        | P200907          | 1       |
| Richter            | Ginger, peeled           | KR27992          | 1       |
| Richter            | Ground ivy herb, cut     | s99/09           | 1       |
| Richter            | Horse chestnut flower... | s-09/09          | 1       |
| Richter            | Lungwort herb, cut       | P195884          | 1       |
| Richter            | Maize style, cut         | B189316          | 1       |
| Richter            | Red-rose petal, cut      | P236157          | 1       |
| Richter            | Tormentil                | P209904          | 1       |
| Rondell Apotheke   | Caffeine citrate         | 15A05-B03-307309 | 1       |
| Safic              | Amygdalin                | 12121302         | 1       |
| Safic Alcan        | Amygdalin                | 150117           | 1       |
| SAFICALCAN         | Amygdalin                | 13041202/2.Tonne | 1       |
| SAFICALCAN         | Amygdalin                | 120141701        | 1       |
| SAFICALCAN         | Amygdalin                | Test3.3.14       | 1       |
| SAFICALCAN         | Amygdalin                | BatchATA08041002 | 1       |
| SAFICALCAN         | Amygdalin                | 13041202/1.Tonne | 1       |
| SAFICALCAN         | Dimercaptosuccinic acid  | 20140618         | 1       |
| SAFICALCAN         | Glycyrrhizic acid        | 11592            | 1       |

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| Supplier                   | Substance                | Batch          | Spectra |
|----------------------------|--------------------------|----------------|---------|
| Safic-Alcan Deutschla. ... | Amygdalin                | 18012-AD/1     | 1       |
| Safic-Alcan Deutschla. ... | Amygdalin                | 17937-AA/1     | 1       |
| Salfic-Alcan               | Amygdalin                | BAE-150610     | 2       |
| Salfic-Alcan               | Amygdalin                | NSMPK06211-BAE | 1       |
| sana 09.12.14 3,75         | Guaiacum wood, cut       | 13343802       | 1       |
| Sana 21.10.14 Ek 3.57      | Maize style, cut         | 13381603       | 2       |
| sanacorp                   | Aniseed                  | 15398602       | 4       |
| sanacorp                   | Artichoke leaf, cut      | 12173301       | 1       |
| sanacorp                   | Caraway fruit            | 2656259        | 1       |
| sanacorp                   | Dandelion herb with r... | 11030310       | 1       |
| sanacorp                   | Maize style, cut         | 10034711       | 1       |
| sanacorp                   | Mallow flower, cut       | 10357906       | 1       |
| sanacorp                   | Marjoram herb, rubbed    | 11212701       | 1       |
| sanacorp                   | Meadowsweet flower, r... | 10349304       | 1       |
| sanacorp                   | Melilot herb, cut        | 10335409       | 1       |
| sanacorp                   | Mullein flower, cut      | 11020706       | 1       |
| sanacorp                   | Nettle leaf, cut         | 12184705       | 1       |
| sanacorp                   | Passionflower herb, cut  | 11049107       | 1       |
| sanacorp                   | Red-rose petal, cut      | 10306512       | 1       |
| sanacorp                   | Rose hips with peel, ... | 10281015       | 1       |
| sanacorp                   | Rosemary leaf, cut       | 12221705       | 1       |
| sanacorp                   | Sage leaf, cut           | 11056123       | 7       |
| sanacorp                   | Shepherd's purse, cut    | 11010505       | 1       |
| sanacorp                   | Solanum dulcamara ste... | 9354603        | 1       |
| sanacorp                   | Verbena herb, cut        | 12188201       | 1       |
| Sanacorp                   | Agnus castus fruit       | 12274006       | 3       |
| Sanacorp                   | Agnus castus fruit       | 12274008       | 2       |
| Sanacorp                   | Alchemilla, cut          | 12153309       | 21      |
| Sanacorp                   | Aluminium chloride he... | 1210014-02     | 28      |
| Sanacorp                   | Aluminium potassium s... | 12184402       | 2       |
| Sanacorp                   | Amphetamine sulfate      | 12/24-N03      | 1       |
| Sanacorp                   | Bearberry leaf, cut      | 2391B110209    | 3       |
| Sanacorp                   | Betony herb, cut         | 13048903       | 4       |
| Sanacorp                   | Bilberry leaf, cut       | 2191A130410    | 2       |
| Sanacorp                   | Caraway fruit            |                | 2       |
| Sanacorp                   | Dandelion herb with r... | 13108803       | 3       |
| Sanacorp                   | Equisetum stem, cut      | 13344307       | 1       |
| Sanacorp                   | European golden rod, ... | 12343103       | 1       |
| Sanacorp                   | Feverfew herb, cut       | 12380201       | 3       |
| Sanacorp                   | Goat's rue, cut          | 12017911       | 1       |
| Sanacorp                   | Hyssop herb, cut         | 13336101       | 6       |
| Sanacorp                   | Juniper                  | 12330509       | 1       |
| Sanacorp                   | Kelp, cut                | 11351105       | 1       |
| Sanacorp                   | Ladys bedstraw herb,...  | 12369003       | 10      |
| Sanacorp                   | Ladys bedstraw herb,...  | 11265109       | 1       |
| Sanacorp                   | Lime flower, cut         | 264045         | 1       |
| Sanacorp                   | Lycopodium herb, cut     | 13101502       | 2       |
| Sanacorp                   | Matricaria flower        | 12294809       | 3       |
| Sanacorp                   | Matricaria flower        | 1300A120725    | 2       |
| Sanacorp                   | Matricaria flower        | 12294804       | 6       |
| Sanacorp                   | Methadone hydrochloride  | 12171913       | 1       |
| Sanacorp                   | Methadone hydrochloride  | 12344806       | 2       |
| Sanacorp                   | Nettle leaf, cut         | 12184707       | 12      |
| Sanacorp                   | Nettle root, cut         | 11265001       | 2       |
| Sanacorp                   | Nettle seed              | 13010602       | 1       |
| Sanacorp                   | Raspberry leaf, cut      | 13101604       | 3       |
| Sanacorp                   | Raspberry leaf, cut      | 13038001       | 7       |
| Sanacorp                   | Roselle                  | 12267508       | 2       |
| Sanacorp                   | Senna leaf, cut          | 13136701       | 4       |
| Sanacorp                   | Sodium hydrogen carbo... | 12D11-N02      | 15      |

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| Supplier                  | Substance                | Batch           | Spectra |
|---------------------------|--------------------------|-----------------|---------|
| Sanacorp                  | Sodium monohydrogenph... | 12345013        | 6       |
| Sanacorp                  | Tormentil                | 12040712        | 3       |
| Sanacorp                  | Wild pansy, cut          | 278106          | 2       |
| Sanacorp                  | Wild pansy, cut          | 12221-01694     | 1       |
| Sanacorp                  | Wormwood herb, cut       | 12103002        | 2       |
| sanacorp,                 | Methadone hydrochloride  | 16135302        | 1       |
| Sanacorp, 6.7.15; 1.70EUR | Oak bark, cut            | 14277002        | 1       |
| sanacorp;3,32;18.06.15    | Coriander                | 13299495        | 1       |
| Siegfried Ltd, Divisi...  | Methadone hydrochloride  | 15244712        | 1       |
| siehe WE-Prüfprotokoll    | 8-quinolinol sulfate ... | 96/09           | 1       |
| Sigma-Aldrich             | Sodium butyrate          | Lot .091M-5302V | 1       |
| Sigma-Aldrich             | Sodium propionate        | SLBK5249V       | 1       |
| Sino Phyto                | Myrrh                    | 90001070        | 1       |
| Sino Phyto                | Rose hips peel, cut      | 1290142         | 1       |
| Spangro/gepepharm         | Bitter fennel            | 15007602        | 1       |
| Spangropharm              | Matricaria flower        | 11169606        | 2       |
| Spangropharm              | Mistletoe, cut           | 10273408        | 1       |
| Spinnrad                  | Black cumin seed         | 11931059        | 1       |
| Spinnrad/Phoenix          | Black cumin seed         | 613310592       | 1       |
| Stefes                    | Tocomax 20%              | 30613           | 1       |
| Stefes                    | Tocomax 20%              | 111013          | 1       |
| stumpf                    | Magnesium chloride he... | 1301c012-277804 | 1       |
| Symrise                   | D-(+)-mannose            |                 | 1       |
| Synop                     | Morphine hydrochloride   | 15I09-B08       | 1       |
| Synopharm                 | Cocaine hydrochloride    | 16B11-B05       | 1       |
| Synopharm am 10.09.2012   | Methadone hydrochloride  | 12B21-No3       | 1       |
| Testmessung               | Amygdalin                | 13011101        | 1       |
| Testmessung               | Amygdalin                | 13041201        | 3       |
| Testmessung               | Amygdalin                | 13041202        | 1       |
| Th. Geyer                 | Amphetamine sulfate      | PH10051         | 1       |
| Th. Geyer                 | Amphetamine sulfate      | 56047           | 1       |
| Th. Geyer                 | Amphetamine sulfate      | 67002           | 51      |
| Th. Geyer                 | Amphetamine sulfate      | 21082013B       | 1       |
| Th. Geyer                 | Amphetamine sulfate      | 67043           | 13      |
| Th. Geyer                 | Calcium colamine phos... | 14384           | 2       |
| Th. Geyer                 | Calcium colamine phos... | 260EXP1016      | 1       |
| Th. Geyer                 | Calcium colamine phos... | 33299           | 1       |
| Th. Geyer                 | Calcium colamine phos... | 7664            | 1       |
| Th. Geyer                 | Codeine phosphate hem... | 67054           | 1       |
| Th. Geyer                 | Codeine phosphate hem... | 67038           | 2       |
| Th. Geyer                 | Dihydrocodeine hydrog... | 67035           | 2       |
| Th. Geyer                 | Dihydrocodeine hydrog... | 59819           | 1       |
| Th. Geyer                 | Methadone hydrochloride  | 67049           | 1       |
| Th. Geyer                 | Methadone hydrochloride  | 67047           | 3       |
| Th. Geyer                 | Methadone hydrochloride  | 67055           | 1       |
| Th. Geyer                 | Morphine hydrochloride   | 1415E-01879     | 1       |
| Th. Geyer                 | Morphine hydrochloride   | 2615M-01879     | 1       |
| Th. Geyer                 | Morphine hydrochloride   | PH120087        | 1       |
| Th. Geyer                 | Morphine hydrochloride   | 67036           | 5       |
| Th. Geyer                 | Phenobarbital            | 67045           | 2       |
| unbekannt                 | Magnesium chloride he... | unbekannt       | 1       |
| Unisa                     | Inositol hexanicotinate  | 22901           | 1       |
| Unisan                    | D-ribose                 | JXCZSJ13D-013   | 2       |
| VDL                       | Basil, rubbed            | 12007004        | 1       |
| VDL                       | Boldo leaf, cut          | 11016503        | 1       |
| VDL                       | Equisetum stem, cut      | 10328914        | 1       |
| VDL                       | Primrose flower          | 11206806        | 1       |
| VDL                       | Yellow chaste weed, cut  | 10244406        | 1       |
| VDL;15.06.15;6,83EUR      | Caraway fruit            | 13306007        | 1       |
| vedono                    | Aniseed, powdered        | 11306208        | 1       |

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| Supplier        | Substance               | Batch     | Spectra |
|-----------------|-------------------------|-----------|---------|
| vedono          | Frankincense            | 12120012  | 1       |
| vedono          | Frankincense            | 12120009  | 5       |
| vedono          | Rhubarb, cut            | 12211907  | 6       |
| vedono          | Roselle                 | 12007313  | 1       |
| vedono          | Wild thyme, cut         | 11374807  | 2       |
| Weltecke        | Meadowsweet herb, cut   | 67010413  | 1       |
| Weltecke        | Thyme, rubbed           | 67101212  | 1       |
| Weltecke / GEHE | Primrose flower         | 63011112  | 1       |
| Wolf            | Alchemilla, cut         | B-698     | 2       |
| Wolf            | Alchemilla, cut         | p931      | 1       |
| Wolf            | Alchemilla, cut         | E-822     | 1       |
| Wolf            | Alchemilla, cut         | 23187     | 4       |
| Wolf            | Aniseed                 | L401F1413 | 1       |
| Wolf            | Aniseed                 | L401F292b | 4       |
| Wolf            | Aniseed                 | B671      | 1       |
| Wolf            | Aniseed                 | 215346    | 1       |
| Wolf            | Aniseed                 | B-671     | 2       |
| Wolf            | Aniseed                 | B216346   | 16      |
| Wolf            | Aniseed                 | 216346    | 1       |
| Wolf            | Bitter fennel           | B-362     | 1       |
| Wolf            | Bitter fennel           | B-682     | 1       |
| Wolf            | Bitter fennel           | B362      | 2       |
| Wolf            | Bitter fennel           | B382      | 1       |
| Wolf            | Bitter fennel           | B-492     | 5       |
| Wolf            | Bitter fennel           | B-493     | 1       |
| Wolf            | Bitter fennel           | B492      | 1       |
| Wolf            | Black cumin seed        | L402F171b | 3       |
| Wolf            | Black cumin seed        | 20720     | 8       |
| Wolf            | Black cumin seed        | L310F141b | 6       |
| Wolf            | Black cumin seed        | B-471     | 1       |
| Wolf            | Black cumin seed        |           | 1       |
| Wolf            | Black cumin seed        | L402F1713 | 1       |
| Wolf            | Black cumin seed        | 207204    | 1       |
| Wolf            | Calendula flower        | 23342     | 1       |
| Wolf            | Caraway fruit           | B-224     | 1       |
| Wolf            | Dill fruit              | L30057    | 5       |
| Wolf            | Dill fruit              | 23622     | 6       |
| Wolf            | Dill fruit              | E-501     | 1       |
| Wolf            | Elder flower, rubbed    | 22749     | 2       |
| Wolf            | Elder flower, rubbed    | 22765     | 1       |
| Wolf            | Elder flower, rubbed    | B-810     | 1       |
| Wolf            | Elder flower, rubbed    | E-738     | 1       |
| Wolf            | Equisetum stem, cut     | B-695     | 1       |
| Wolf            | Equisetum stem, cut     | B233885   | 4       |
| Wolf            | Lemon grass, cut        | B654      | 1       |
| Wolf            | Lemon verbena leaf, cut | 23635     | 1       |
| Wolf            | Lemon verbena leaf, cut | B-312     | 1       |
| Wolf            | Lemon verbena leaf, cut | E-587     | 1       |
| Wolf            | Lime flower, cut        | 22094     | 1       |
| Wolf            | Lime flower, cut        | B449      | 1       |
| Wolf            | Marjoram herb, rubbed   | B163516   | 6       |
| Wolf            | Marjoram herb, rubbed   | P232243   | 9       |
| Wolf            | Marjoram herb, rubbed   | 163516    | 1       |
| Wolf            | Matricaria flower       | 23242     | 1       |
| Wolf            | Nettle leaf, cut        | P234605   | 10      |
| Wolf            | Nettle leaf, cut        | B-821     | 1       |
| Wolf            | Nettle leaf, cut        | B821      | 1       |
| Wolf            | Peppermint leaf, cut    | B-185     | 5       |
| Wolf            | Peppermint leaf, cut    | P221379   | 7       |
| Wolf            | Peppermint leaf, cut    | B-725     | 2       |

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| Supplier                 | Substance                | Batch       | Spectra |
|--------------------------|--------------------------|-------------|---------|
| Wolf                     | Peppermint leaf, cut     | B243        | 1       |
| Wolf                     | Peppermint leaf, cut     | B-120       | 1       |
| Wolf                     | Peppermint leaf, cut     | B725        | 1       |
| Wolf                     | Raspberry leaf, cut      | B-457       | 1       |
| Wolf                     | Raspberry leaf, cut      | P201727     | 19      |
| Wolf                     | Raspberry leaf, cut      | P222676     | 1       |
| Wolf                     | Sage leaf, cut           | B735        | 1       |
| Wolf                     | Shepherd's purse, cut    | B449        | 2       |
| Wolf                     | St. John's wort, cut     | B206152     | 1       |
| Wolf                     | St. John's wort, cut     | 19468       | 2       |
| Wolf                     | St. John's wort, cut     | 206152      | 1       |
| Wolf                     | St. John's wort, cut     | B-424       | 2       |
| Wolf                     | St. John's wort, cut     | B-455       | 2       |
| Wolf                     | Yarrow herb, cut         | B230010     | 9       |
| Wolf                     | Yarrow herb, cut         | 230010      | 1       |
| Xi'An Chongxin Natura... | Amygdalin                | 13031401    | 1       |
| -                        | Angelica root            | 130924      | 1       |
| 10.2011                  | Aniseed                  | 10247201    | 1       |
| -                        | Bitter orange flower ... | 2011A-01445 | 1       |
| -                        | Burdock root, cut        | 5110I-02131 | 1       |
| 21.08.2013               | Calendula flower         | 1241130321  | 1       |
| -                        | Chelidonium majus her... | 810I-01632  | 1       |
| -                        | Chickweed, cut           | 2011A-01686 | 1       |
| -                        | Chicory herb, cut        | 4411I-01634 | 1       |
| -                        | Elecampane rhizome, cut  | 712M-02181  | 1       |
| -                        | Gentian root, powdered   | 130063      | 1       |
| 1351 B 111207            | Hawthorn flower          | 1351B111207 | 4       |
| 5N Plus Lübeck GmbH/ ... | Heavy alkaline bismut... | 12146908    | 1       |
| -                        | Iceland moss, cut        | 4711E-01774 | 1       |
| 20; 09.11.2013           | Marshmallow root, pee... | 13057105    | 1       |
| -                        | Meadowsweet herb, cut    | 130849      | 1       |
| -                        | Meadowsweet herb, cut    | 1511M-01685 | 1       |
| -                        | Melilot herb, cut        | 811Q-01664  | 1       |
| -                        | Melissa leaf, cut        | 131146      | 1       |
| -                        | Raspberry leaf, cut      | 130849      | 1       |
| -                        | Silverweed, cut          | 130849      | 1       |
| -                        | Silverweed, cut          | 711M-01619  | 1       |
| -                        | Wild thyme, cut          | 131023      | 1       |
| -                        | Wild thyme, cut          | 130685      | 1       |



## Appendix D: Requirements of validation

In order to ensure adherence to the safe scientific status, the individual methods for manufacturing and testing must be validated under certain circumstances (compare § 34 para. 1 no. 3, § 35 para. 1 no. 4 and para. 4 sentence 1 no. 2 b, para. 6 sentence 3 *ApoBetrO* [Pharmacies Rules and Regulations]). The *ApoBetrO* [Pharmacies Rules and Regulations] incorporates a legal definition in § 1 a para. 16 (quotation translated):

*“Validation is the provision of documented proof which with a high degree of safety documents that, via a specific process or standard work process, a medicinal product is manufactured and tested, which is in accordance with previously determined quality features.”*

Validation documentation can be used to prove that methods or devices which are not described in the Pharmacopoeia within the meaning of § 6 para. 1 sentence 3 *ApBetrO* [Pharmacies Rules and Regulations] achieve the same results as those in the Pharmacopoeia. On the other hand, with the requirements of the demanded validation it must be observed whether the respective testing method is already incorporated in the Pharmacopoeia.

NIR spectroscopy as a general testing method need not be validated in accordance with the express ruling in the *Ph. Eur. Section 1.1* [3], as it is already described in *Section 2.2.40* of the *Ph. Eur.* as an area of application for the identification of raw materials.

However, a special validation requirement exists for the reference database. This requirement is met with the existing document. Further requirements or rules as to how this proof must be furnished do not exist. It is required that the processes guarantee the same results as the methods and devices in the Pharmacopoeia [17].

Carrying out identity tests with *Apo-Ident* is therefore also possible if the NIR spectroscopy process is not required in the Pharmacopoeia monograph of the substance for identity testing. All NIR analyses with *Apo-Ident* prove several, often all molecule groups and are therefore comparable with a series of individual, targeted chemical proofs [4]. Therefore, the identity proof with *Apo-Ident* replaces the monograph test series (with two or more test combinations).

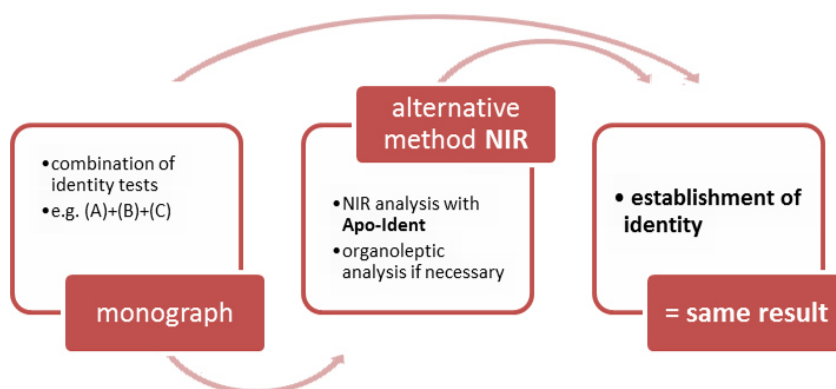


**Figure 2:** The combination of tests of the monograph is replaced by the alternative method NIR spectroscopy using *Apo-Ident*. This is permissible because both test procedures result in the establishment of the identity of the raw material.

With this validation documentation, proof is furnished that identical results are achieved with *Apo-Ident* and Pharmacopoeia methods, i.e. confirmation of the identity of the raw material [2].

## ***Appendix E: Conformity of Apo-Ident with the European pharmacopeia***

According to *Ph. Eur. Section 2.2.40*, NIR spectroscopy is basically suitable for: “Identification of agents, excipients, dosage forms, intermediate manufacturing products, chemical raw materials and packaging materials” ([3], quotation translated).

The fact that *Apo-Ident* meets the further criteria of the European Pharmacopoeia under the headings in *Section 2.2.40*

- Apparatus
- Measurement methods
- Sample preparation and presentation
- Testing the functionality of the instrument
- Identification and characterisation (qualitative analysis)
- Quantitative analysis
- Ongoing model evaluation
- Transfer of databases
- Data storage

can be proven based on the *HiperScan GmbH* documentation of “Meeting 2.2.40 *Ph. Eur.* by *Apo-Ident*” [4].

## **Anhang F: Zusatz zu den Modellen der zweiten Stufe**

Wie im allgemeinen Teil der Validierungsdokumentation des *Apo-Ident* im Abschnitt [Ablauf von Modellerstellung und Validierungsläufen](#) unter 2. *Generieren der chemometrischen Modelle (Kalibrierung)* in f) beschrieben, besteht die Möglichkeit für bestimmte Substanzen ein weiteres *chemometrisches Modell* zu erstellen (Zweite-Stufe-Modell) und die Bewertung in mehreren Stufen vorzunehmen.

### **Substanzen in Stufe-Zwei-Modellen**

Im *Apo-Ident Update 2018-01* werden folgende Substanzen in den aufgeführten Stufe-Zwei-Modellen differenziert:

#### ***Submodell 1***

Betamethason, mikronisiert  
Betamethasonvalerat  
Budesonid, mikronisiert  
Dexamethason  
Erythromycin  
Hydrocortisonbutyrat  
Norethisteronacetat  
Prednicarbat, mikronisiert  
Prednisolon, mikronisiert  
Triamcinolonacetonid

#### ***Submodell 2***

Beclometasondipropionat, wasserfreies  
Betamethasondipropionat, mikronisiert  
Clobetasolpropionat  
Diphenylcyclopropenon  
Gentamicinsulfat  
Natriumbenzoat  
Natriumcitrat  
Oxybutyninhydrochlorid

#### ***Submodell 3***

Alfatradiol  
Chininhydrochlorid  
Chininsulfat Dihydrat  
Estriol  
Pregnenolon  
Progesteron, mikronisiert  
Spironolacton  
Testosteronpropionat

#### ***Submodell flüssig***

2-Ethylhexyllaurat  
Basiscreme DAC  
Hydrophile Creme, nichtionisch DAB  
Lanette®-Salbe (konserviert)  
Squalan  
Wollwachsalkoholcreme DAB/SR





## References

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Tetracaine base, [1491](#)

Tetracaine hydrochloride, [1497](#)

Tetracaini hydrochloridum, *see* [Tetracaine hydrochloride](#)

Tetracainum, *see* [Tetracaine base](#)

Tetracainum hydrochloricum, *see* [Tetracaine hydrochloride](#)

Tetracycline hydrochloride, [1505](#)

Tetracyclini hydrochloridum, *see* [Tetracycline hydrochloride](#)

Tetracyclinum hydrochloricum, *see* [Tetracycline hydrochloride](#)

Thalidomide, [1511](#)

Thalidomidum, *see* [Thalidomide](#)

Theophylline, [1515](#)

Theophylline-ethylenediamine hydrate, [1519](#)

Theophyllinum, *see* [Theophylline](#)

Theophyllinum aethylendiaminum hydricum, *see* [Theophylline-ethylenediamine hydrate](#)

Theophyllinum et ethylenediaminum

hydricum, *see*

[Theophylline-ethylenediamine hydrate](#)

Thiamine chloride hydrochloride, [1523](#)

Thiamini hydrochloridum, *see* [Thiamine chloride hydrochloride](#)

Threoninum, *see* [L-threonine](#)

Thymol, [1527](#)

Thymolum, *see* [Thymol](#)

Tobramycin sulfate, [1531](#)

Tobramycin sulphate, *see* [Tobramycin sulfate](#)

Tobramycini sulfas, *see* [Tobramycin sulfate](#)

Tobramycinum sulfuricum, *see* [Tobramycin sulfate](#)

Tosylchloramide sodium, [1535](#)

Tosylchloramidum natricum, *see*

[Tosylchloramide sodium](#)

Tranexamic acid, [1539](#)

Tretinoin, [1543](#)

Tretinoinum, *see* [Tretinoin](#)

Triamcinolon, micronized, [1551](#)

Triamcinolone acetone, [1555](#)

Triamcinoloni acetonidum, *see* [Triamcinolone acetone](#)

Triamcinolonum acetone, *see*

[Triamcinolone acetone](#)

Triamcinolonum micronisatum, *see*

[Triamcinolon, micronized](#)

Triclosan, [1567](#)

Triclosanum, *see* [Triclosan](#)

Tritici amylum, *see* [Starch](#)

Trometamol, [1581](#)

Trometamolum, *see* [Trometamol](#)

Tropicamide, [1587](#)

Tropicamidum, *see* [Tropicamide](#)

Tryptophanum, *see* [L-tryptophan](#)

Tyrosine, [1591](#)

Tyrosinum, *see* [Tyrosine](#)

Tyrothricin, [1595](#)

Tyrothricinum, *see* [Tyrothricin](#)

Ubidecarenone, [1599](#)

Ubidecarenonum, *see* [Ubidecarenone](#)

Urea, [1603](#)

Urea pura, *see* [Urea](#)

Ureum, *see* [Urea](#)

Uridine, [1613](#)

Uridinum, *see* [Uridine](#)

Valine, [1617](#)

Valinum, *see* [Valine](#)

Vancomycin hydrochloride, [1621](#)

Vancomycini hydrochloridum, *see* [Vancomycin hydrochloride](#)

Vanillin, [1625](#)

Vanillinum, *see* [Vanillin](#)

Wax, bleached, *see* [Waxes / Fats](#)

Wax, yellow, *see* [Waxes / Fats](#)

Waxes / Fats, [1629](#)

Wheat starch, *see* [Starch](#)

Wool alcohols, [1645](#)

Xylitol, [1649](#)

Xylitolum, *see* [Xylitol](#)

Xylometazoline hydrochloride, [1653](#)

Xylometazolini hydrochloridum, *see* [Xylometazoline hydrochloride](#)

Xylometazolinum hydrochloricum, *see* [Xylometazoline hydrochloride](#)

Xylose, [1657](#)

Xylosum, *see* [Xylose](#)

Zinc acetate dihydrate, [1661](#)

Zinc gluconate, [1665](#)

Zinci acetate dihydricus, *see* [Zinc acetate dihydrate](#)

Zinci gluconas, *see* [Zinc gluconate](#)

Zincum aceticum purum, *see* [Zinc acetate](#)

[dihydrate](#)

Zincum gluconicum, *see* [Zinc gluconate](#)