

# Validation documentation

## *BioG MicroTabs*

HiperScan GmbH

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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 *BioG MicroTabs*.

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 *BioG MicroTabs*. 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 *BioG MicroTabs* 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, em 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*”.

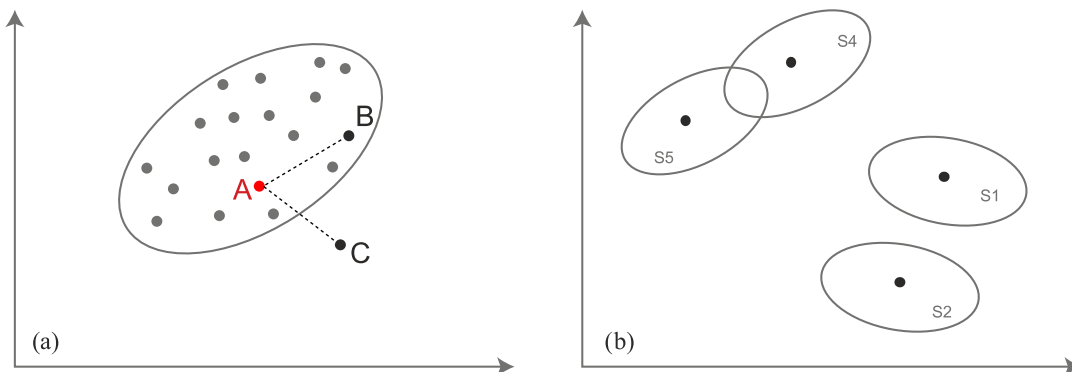
**The ‘Rule of Three’** says that with a probability of 95 % the next random sample of the same size no more than three false results are to be expected if no false result existed in the existing random sample [10, 11].

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 *S*<sub>4</sub> and *S*<sub>5</sub> is smaller than between *S*<sub>1</sub> and *S*<sub>2</sub>. 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 6383 spectra from 90 different batches for a total of 62 substances were used to validate the substance class *BioG MicroTabs*.

### 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
BioG MicroTabs	20	21	1634

From category *A* a total of 1634 spectra from 21 batches for a total of 20 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
BioG MicroTabs	62	87	4710

From category *B* a total of 4710 spectra from 87 batches for a total of 62 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
BioG MicroTabs	12	12	39

From category *C* a total of 39 spectra from 12 batches for a total of 12 substances were taken into account for validation.

### Validation results

The validation runs checked whether all substances/substance groups in the substance class *BioG MicroTabs* 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 *BioG MicroTabs* 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
Type A	0	1634	0	27 778
Type B	0	972	748	83 044
Type C	0	7	11	676

All substances/substance groups in the substance class *BioG MicroTabs* 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
Type A	100.000 00 % (> 99.976 98 %)	100.000 00 % (> 99.585 56 %)
Type B	100.000 00 % (> 99.990 33 %)	65.174 35 % (> 64.932 30 %)
Type C	100.000 00 % (> 98.839 39 %)	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.

# VALIDATION REPORT

## IdentModul 1.3-2017-06

Validated substance/substance group	Activated B-complex / Methylcobalamin / Vitamin D3
Substance class	BioG MicroTabs
Report date	17/11/2017
Report number	90073-2017-11-17
Executing company	HiperScan GmbH Weißeritzstraße 3 01067 Dresden Germany

### Relevant substance names

Activated B-complex / Methylcobalamin / Vitamin D3; Activated B-complex; Methylcobalamin; Vitamin D3

### Special notes

When selecting the *Activated B-complex / Methylcobalamin / Vitamin D3* 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 *Activated B-complex / Methylcobalamin / Vitamin D3*:

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenics	Activated B-comp...	BG15013	90073	40	from supplier
Biogenics	Vitamin D3	305411	90074	40	from supplier
Biogenics	Methylcobalamin	HK8001	90078	40	from supplier
Biogenics	Activated B-comp...	BG15013	90087	40	from supplier

*continued on the next page*

continued from previous page

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenics	Vitamin D3	306411	90088	40	from supplier
Biogenics	Vitamin D3	305411	90095	40	from supplier
Biogenics	Methylcobalamin	HK8001	90101	40	from supplier

## Validation samples

A total of 6383 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 *Activated B-complex / Methylcobalamin / Vitamin D3*. These samples are listed above in the [calibration samples](#) section.
- 1354 spectra from a total of 17 batches from further 17 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

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

- 220 spectra of 9 reference samples from the substance/substance group *Activated B-complex / Methylcobalamin / Vitamin D3*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenics	Vitamin D3	HK8002	90066	40
Biogenics	Methylcobalamin	HK8001	90069	40
Biogenics	Activated B-complex	BG15013	90073 <sup>†</sup>	20
Biogenics	Vitamin D3	305411	90074 <sup>†</sup>	20
Biogenics	Methylcobalamin	HK8001	90078 <sup>†</sup>	20
Biogenics	Activated B-complex	BG15013	90087 <sup>†</sup>	20
Biogenics	Vitamin D3	306411	90088 <sup>†</sup>	20
Biogenics	Vitamin D3	305411	90095 <sup>†</sup>	20
Biogenics	Methylcobalamin	HK8001	90101 <sup>†</sup>	20

- 4490 spectra from a total of 52 batches from further 59 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance

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

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

**Type C** Spectra of independent samples not included in the database structure. *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 *Activated B-complex / Methylcobalamin / Vitamin D3*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

### Validation results

The validation runs checked whether the substance/substance group *Activated B-complex / Methylcobalamin / Vitamin D3* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Activated B-complex / Methylcobalamin / Vitamin D3* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected 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	1354
<b>Type B</b>	0	190	30	4490
<b>Type C</b>	0	0	0	39

The substance/substance group *Activated B-complex / Methylcobalamin / Vitamin D3* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5682 %)	100.0000 % (> 97.8571 %)
<b>Type B</b>	100.0000 % (> 99.8242 %)	86.3636 % (> 85.0000 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90073	90073	0.00	51.00
90074	90074	0.00	52.67
90078	90078	0.00	51.75
90087	90087	0.00	50.44
90088	90088	0.00	49.48
90095	90095	0.00	52.17
90101	90101	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 1.3-2017-06

Validated substance/substance group **alpha lipoic acid**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90077-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

alpha lipoic acid; a-lipoic acid

### Special notes

When selecting the *alpha lipoic 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 *alpha lipoic acid*:

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenerics	alpha lipoic acid	134505	90077	40	from supplier
Biogenerics	alpha lipoic acid	134505	90102	40	from supplier

## Validation samples

A total of 6383 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 *alpha lipoic acid*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *alpha lipoic acid*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenerics	alpha lipoic acid	134505	90077 <sup>†</sup>	20
Biogenerics	alpha lipoic acid	134505	90102 <sup>†</sup>	20

- 4670 spectra from a total of 56 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *alpha lipoic acid*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in 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 *alpha lipoic 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 *alpha lipoic 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	1554
<b>Type B</b>	0	40	0	4670
<b>Type C</b>	0	0	0	39

The substance/substance group *alpha lipoic 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 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8276 %)	100.0000 % (> 85.0000 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90077	90077	0.00	136.07
90102	90102	0.00	134.35

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 1.3-2017-06

Validated substance/substance group **AMP max**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90111-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

AMP max

### Special notes

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

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

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

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenics	AMP max	CNP011215A	90111	40	from supplier
Biogenics	AMP max	CNP011215A	90112	40	from supplier

## Validation samples

A total of 6383 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 *AMP max*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *AMP max*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenerics	AMP max	CNP011215A	90111 <sup>†</sup>	20
Biogenerics	AMP max	CNP011215A	90112 <sup>†</sup>	20

- 4670 spectra from a total of 56 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *AMP max*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in 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 *AMP max* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *AMP max* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected 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	1554
<b>Type B</b>	0	30	10	4670
<b>Type C</b>	0	0	0	39

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

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8276 %)	75.0000 % (> 67.5000 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90111	90111	0.00	23.85
90112	90112	0.00	28.39

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 1.3-2017-06

Validated substance/substance group **Andrographis**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90000-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Andrographis

### Special notes

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

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

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

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenics	Andrographis	GD8001	90103	40	from supplier
Biogenics	Andrographis	GD8001	90104	40	from supplier

## Validation samples

A total of 6383 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 *Andrographis*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *Andrographis*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenerics	Andrographis	GD8001	90000	40
Biogenerics	Andrographis	GD8001	90056	40
Biogenerics	Andrographis	GD8001	90103 <sup>†</sup>	20
Biogenerics	Andrographis	GD8001	90104 <sup>†</sup>	20

- 4590 spectra from a total of 56 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 1 batches from the substance/substance group *Andrographis*.

Supplier	Substance	Batch	Spectra
Direkt	Andrographis	GD8001	2

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

- 37 spectra from 1 *Apo-Ident* customers from a total of 11 batches from a further 11 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Andrographis* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Andrographis* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected 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	1554
<b>Type B</b>	0	40	80	4590
<b>Type C</b>	0	2	0	37

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

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8248 %)	33.3333 % (> 30.8333 %)
<b>Type C</b>	100.0000 % (> 80.8658 %)	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
90103	90103	0.00	23.44
90104	90104	0.00	24.23

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 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 1.3-2017-06

Validated substance/substance group **Boswellia**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90004-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Boswellia

### Special notes

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

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

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

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenerics	Boswellia	BG15260	90072	40	from supplier
Biogenerics	Boswellia	BG15260	90098	40	from supplier

## Validation samples

A total of 6383 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 *Boswellia*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *Boswellia*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenerics	Boswellia	GD8002	90004	40
Biogenerics	Boswellia	GD8002	90055	40
Biogenerics	Boswellia	BG15260	90072 <sup>†</sup>	20
Biogenerics	Boswellia	BG15260	90098 <sup>†</sup>	20

- 4590 spectra from a total of 55 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *Boswellia*.

Supplier	Substance	Batch	Spectra
Direkt	Boswellia	GD8002	3

<sup>†</sup>These spectra were recorded from 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 1 *Apo-Ident* customers from a total of 11 batches from a further 11 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Boswellia* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Boswellia* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected 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	1554
<b>Type B</b>	0	40	80	4590
<b>Type C</b>	0	0	3	36

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

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8248 %)	33.3333 % (> 30.8333 %)
<b>Type C</b>	100.0000 % (> 80.1082 %)	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
90072	90072	0.00	127.41
90098	90098	0.00	126.64

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 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 1.3-2017-06

Validated substance/substance group	Calcium/vitamin D3
Substance class	BioG MicroTabs
Report date	17/11/2017
Report number	90080-2017-11-17
Executing company	HiperScan GmbH Weißeritzstraße 3 01067 Dresden Germany

### Relevant substance names

Calcium/vitamin D3

### Special notes

When selecting the *Calcium/vitamin D3* 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/vitamin D3*:

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenerics	Calcium/vitamin D3	BG15243	90080	40	from supplier
Biogenerics	Calcium/vitamin D3	BG15243	90091	45	from supplier

## Validation samples

A total of 6383 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 85 spectra of 2 reference samples from the substance/substance group *Calcium/vitamin D3*. These samples are listed above in the [calibration samples](#) section.
- 1549 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

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

- 95 spectra of 3 reference samples from the substance/substance group *Calcium/vitamin D3*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenics	Calcium/vitamin D3	BG15243	90080 <sup>†</sup>	20
Biogenics	Calcium/vitamin D3	BG15243	90091 <sup>†</sup>	15
Biogenics	Calcium/vitamin D3	BG16102	90128	60

- 4615 spectra from a total of 55 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *Calcium/vitamin D3*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples

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

are listed in the *Type C* section of each substance page. If the substance 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/vitamin D3* can clearly be 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/vitamin D3* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

	False positive	True positive	False negative	True negative
<b>Type A</b>	0	85	0	1549
<b>Type B</b>	0	35	60	4615
<b>Type C</b>	0	0	0	39

The substance/substance group *Calcium/vitamin D3* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5843 %)	100.0000 % (> 92.9412 %)
<b>Type B</b>	100.0000 % (> 99.8252 %)	36.8421 % (> 33.6842 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90080	90080	0.00	75.39
90091	90091	0.00	73.46

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 1.3-2017-06

Validated substance/substance group **Chondroitin sulfate**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90005-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Chondroitin sulfate; Chondroitin sulphate

### Special notes

When selecting the *Chondroitin 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 *Chondroitin sulfate*:

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenics	Chondroitin sulf. ...	JA8004	90071	40	from supplier
Biogenics	Chondroitin sulf. ...	JA8004	90096	40	from supplier

## Validation samples

A total of 6383 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 *Chondroitin sulfate*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

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

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

Supplier	Substance	Batch	Sample ID	Spectra
Biogenics	Chondroitin sulfate	EK0412	90005	40
Biogenics	Chondroitin sulfate	EK0412	90049	40
Biogenics	Chondroitin sulfate	JA8004	90071 <sup>†</sup>	20
Biogenics	Chondroitin sulfate	JA8004	90096 <sup>†</sup>	20

- 4590 spectra from a total of 55 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *Chondroitin sulfate*.

Supplier	Substance	Batch	Spectra
Direkt	Chondroitin sulfate	EK0412	3

<sup>†</sup>These spectra were recorded from 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 1 *Apo-Ident* customers from a total of 11 batches from a further 11 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Chondroitin 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 *Chondroitin 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	1554
<b>Type B</b>	0	53	67	4590
<b>Type C</b>	0	0	3	36

The substance/substance group *Chondroitin 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 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8248 %)	44.1667 % (> 41.6667 %)
<b>Type C</b>	100.0000 % (> 80.1082 %)	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
90071	90071	0.00	39.23
90096	90096	0.00	40.67

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 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 1.3-2017-06

Validated substance/substance group **Curcumax / ginger**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90109-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Curcumax / ginger

### Special notes

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

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

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

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenics	Curcumax / ginger	FJ0187	90109	40	from supplier
Biogenics	Curcumax / ginger	FJ0187	90110	40	from supplier

## Validation samples

A total of 6383 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 *Curcumax / ginger*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *Curcumax / ginger*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenics	Curcumax / ginger	EB0106	90059	40
Biogenics	Curcumax / ginger	FJ0187	90109 <sup>†</sup>	20
Biogenics	Curcumax / ginger	FJ0187	90110 <sup>†</sup>	20

- 4630 spectra from a total of 56 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *Curcumax / ginger*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples

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

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

### Validation results

The validation runs checked whether the substance/substance group *Curcumax / ginger* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Curcumax / ginger* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected 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	1554
<b>Type B</b>	0	40	40	4630
<b>Type C</b>	0	0	0	36

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

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8255 %)	50.0000 % (> 46.2500 %)
<b>Type C</b>	100.0000 % (> 80.1082 %)	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
90109	90109	0.00	62.22
90110	90110	0.00	60.10

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 1.3-2017-06

Validated substance/substance group **Fruit & greens**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90008-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Fruit & greens

### Special notes

When selecting the *Fruit & greens* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

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

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenerics	Fruit & greens	FL0437	90085	40	from supplier
Biogenerics	Fruit & greens	FL0437	90093	40	from supplier

## Validation samples

A total of 6383 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 *Fruit & greens*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *Fruit & greens*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenerics	Fruit & greens	pending	90008	40
Biogenerics	Fruit & greens	FL0437	90085 <sup>†</sup>	20
Biogenerics	Fruit & greens	FL0437	90093 <sup>†</sup>	20

- 4630 spectra from a total of 56 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Fruit & greens*.

Supplier	Substance	Batch	Spectra
Röhr	Fruit & greens	FL0437	5

<sup>†</sup>These spectra were recorded from 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 1 *Apo-Ident* customers from a total of 11 batches from a further 11 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Fruit & greens* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Fruit & greens* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected 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	1554
<b>Type B</b>	0	79	1	4630
<b>Type C</b>	0	5	0	34

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

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8255 %)	98.7500 % (> 95.0000 %)
<b>Type C</b>	100.0000 % (> 79.5022 %)	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
90085	90085	0.00	38.52
90093	90093	0.00	38.08

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 1.3-2017-06

Validated substance/substance group **L-arginine**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90023-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

L-arginine

### Special notes

When selecting the *L-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 *L-arginine*:

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenerics	L-arginine	134514	90105	40	from supplier
Biogenerics	L-arginine	134514	90106	40	from supplier

## Validation samples

A total of 6383 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-arginine*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *L-arginine*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenerics	L-arginine	pending	90023	40
Biogenerics	L-arginine	134514	90105 <sup>†</sup>	20
Biogenerics	L-arginine	134514	90106 <sup>†</sup>	20

- 4630 spectra from a total of 56 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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-arginine*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples

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

are listed in the *Type C* section of each substance page. If the substance 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-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 *L-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	80	0	1554
<b>Type B</b>	0	40	40	4630
<b>Type C</b>	0	0	0	39

The substance/substance group *L-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 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8255 %)	50.0000 % (> 46.2500 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90105	90105	0.00	257.34
90106	90106	0.00	288.95

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 1.3-2017-06

Validated substance/substance group **MSM**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90012-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

MSM

### Special notes

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

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

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

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenerics	MSM	JA8007	90082	44	from supplier
Biogenerics	MSM	JA8007	90094	40	from supplier

## Validation samples

A total of 6383 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 84 spectra of 2 reference samples from the substance/substance group *MSM*. These samples are listed above in the [calibration samples](#) section.
- 1550 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *MSM*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenics	MSM	JA8007	90012	40
Biogenics	MSM	JA8007	90070	40
Biogenics	MSM	JA8007	90082 <sup>†</sup>	15
Biogenics	MSM	JA8007	90094 <sup>†</sup>	20

- 4595 spectra from a total of 56 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *MSM*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within

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

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

## Validation results

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

	False positive	True positive	False negative	True negative
<b>Type A</b>	0	84	0	1550
<b>Type B</b>	0	75	40	4595
<b>Type C</b>	0	0	0	39

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

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5845 %)	100.0000 % (> 92.8571 %)
<b>Type B</b>	100.0000 % (> 99.8249 %)	65.2174 % (> 62.6087 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90082	90082	0.00	248.63
90094	90094	0.00	249.08

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 1.3-2017-06

Validated substance/substance group **MultiVit / Min Plus**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90014-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

MultiVit / Min Plus

### Special notes

When selecting the *MultiVit / Min Plus* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

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

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenetics	MultiVit / Min P...	140134	90086	40	from supplier
Biogenetics	MultiVit / Min P...	140134	90089	45	from supplier

## Validation samples

A total of 6383 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 85 spectra of 2 reference samples from the substance/substance group *MultiVit / Min Plus*. These samples are listed above in the [calibration samples](#) section.
- 1549 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *MultiVit / Min Plus*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenerics	MultiVit / Min Plus	FL0029	90014	40
Biogenerics	MultiVit / Min Plus	FL0029	90053	40
Biogenerics	MultiVit / Min Plus	140134	90086 <sup>†</sup>	20
Biogenerics	MultiVit / Min Plus	140134	90089 <sup>†</sup>	15

- 4595 spectra from a total of 55 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *MultiVit / Min Plus*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within

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

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

## Validation results

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

	False positive	True positive	False negative	True negative
<b>Type A</b>	0	85	0	1549
<b>Type B</b>	0	35	80	4595
<b>Type C</b>	0	0	0	39

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

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5843 %)	100.0000 % (> 92.9412 %)
<b>Type B</b>	100.0000 % (> 99.8249 %)	30.4348 % (> 27.8261 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90086	90086	0.00	57.87
90089	90089	0.00	52.83

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 1.3-2017-06

Validated substance/substance group **N-acetylcysteine**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90034-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

N-acetylcysteine

### Special notes

When selecting the *N-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 *N-acetylcysteine*:

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenerics	N-acetylcysteine	BG15271	90079	40	from supplier

## Validation samples

A total of 6383 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 40 spectra of 1 reference samples from the substance/substance group *N-acetylcysteine*. These samples are listed above in the [calibration samples](#) section.
- 1594 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *N-acetylcysteine*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenics	N-acetylcysteine	2111E-07106	90034	40
Biogenics	N-acetylcysteine	2111E-07106	90045	40
Biogenics	N-acetylcysteine	BG15271	90079 <sup>†</sup>	20
Biogenics	N-acetylcysteine	BG15271	90119	60
Biogenics	N-acetylcysteine	BG16165	90126	60

- 4490 spectra from a total of 54 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *N-acetylcysteine*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within

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

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

### Validation results

The validation runs checked whether the substance/substance group *N-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 *N-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	40	0	1594
<b>Type B</b>	0	80	140	4490
<b>Type C</b>	0	0	0	39

The substance/substance group *N-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 % (> 99.6102 %)	100.0000 % (> 85.0000 %)
<b>Type B</b>	100.0000 % (> 99.8242 %)	36.3636 % (> 35.0000 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90079	90079	0.00	282.64

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 1.3-2017-06

Validated substance/substance group **Prime alpha**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90083-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Prime alpha

### Special notes

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

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

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

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenics	Prime alpha	4057F1	90083	55	from supplier
Biogenics	Prime alpha	4057F1	90099	40	from supplier

## Validation samples

A total of 6383 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 95 spectra of 2 reference samples from the substance/substance group *Prime alpha*. These samples are listed above in the [calibration samples](#) section.
- 1539 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

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

- 40 spectra of 2 reference samples from the substance/substance group *Prime alpha*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenics	Prime alpha	4057F1	90083 <sup>†</sup>	20
Biogenics	Prime alpha	4057F1	90099 <sup>†</sup>	20

- 4670 spectra from a total of 56 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *Prime alpha*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in 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 *Prime alpha* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Prime alpha* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

	False positive	True positive	False negative	True negative
<b>Type A</b>	0	95	0	1539
<b>Type B</b>	0	40	0	4670
<b>Type C</b>	0	0	0	39

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

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5818 %)	100.0000 % (> 93.6842 %)
<b>Type B</b>	100.0000 % (> 99.8276 %)	100.0000 % (> 85.0000 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90083	90083	0.00	31.95
90099	90099	0.00	21.70

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 1.3-2017-06

Validated substance/substance group **Prime alpha plus**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90084-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Prime alpha plus

### Special notes

When selecting the *Prime alpha plus* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

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

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenerics	Prime alpha plus	4058F1	90084	40	from supplier
Biogenerics	Prime alpha plus	4058F1	90100	40	from supplier

## Validation samples

A total of 6383 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 *Prime alpha plus*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

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

- 40 spectra of 2 reference samples from the substance/substance group *Prime alpha plus*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenics	Prime alpha plus	4058F1	90084 <sup>†</sup>	20
Biogenics	Prime alpha plus	4058F1	90100 <sup>†</sup>	20

- 4670 spectra from a total of 56 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *Prime alpha plus*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in 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 *Prime alpha plus* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Prime alpha plus* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected 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	1554
<b>Type B</b>	0	40	0	4670
<b>Type C</b>	0	0	0	39

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

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8276 %)	100.0000 % (> 85.0000 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90084	90084	0.00	20.29
90100	90100	0.00	16.32

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 1.3-2017-06

Validated substance/substance group **Q10 emblica**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90018-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Q10 emblica

### Special notes

When selecting the *Q10 emblica* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Q10 emblica*:

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenics	Q10 emblica	BG15105	90075	40	from supplier
Biogenics	Q10 emblica	BG15105	90092	40	from supplier

## Validation samples

A total of 6383 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 *Q10 emblica*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *Q10 emblica*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenerics	Q10 emblica	BG15105	90075 <sup>†</sup>	20
Biogenerics	Q10 emblica	BG15105	90092 <sup>†</sup>	20

- 4670 spectra from a total of 56 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *Q10 emblica*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in 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 *Q10 emblica* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Q10 emblica* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected 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	1554
<b>Type B</b>	0	40	0	4670
<b>Type C</b>	0	0	0	39

The substance/substance group *Q10 emblica* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8276 %)	100.0000 % (> 85.0000 %)
<b>Type C</b>	100.0000 % (> 78.5931 %)	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
90075	90075	0.00	28.73
90092	90092	0.00	21.05

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 1.3-2017-06

Validated substance/substance group **Red rice extract 3%**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90076-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Red rice extract 3%

### Special notes

When selecting the *Red rice extract 3%* substance/substance group, the following information is displayed to the user:

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

Only spectra which have been recorded by *HiperScan GmbH* from traceable samples are used for the generation of the [chemometric models](#). The following samples have been obtained from the substance/substance group *Red rice extract 3%*:

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenerics	Red rice extract...	46501	90076	40	from supplier
Biogenerics	Red rice extract...	46501	90090	45	from supplier

## Validation samples

A total of 6383 spectra were provided for validation. The results were evaluated separately according to the following sample categories:

### Type A All calibration spectra.

- 85 spectra of 2 reference samples from the substance/substance group *Red rice extract 3%*. These samples are listed above in the [calibration samples](#) section.
- 1549 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

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

- 35 spectra of 2 reference samples from the substance/substance group *Red rice extract 3%*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenics	Red rice extract 3%	46501	90076 <sup>†</sup>	20
Biogenics	Red rice extract 3%	46501	90090 <sup>†</sup>	15

- 4675 spectra from a total of 57 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 *Red rice extract 3%*.
- 39 spectra from 1 *Apo-Ident* customers from a total of 12 batches from a further 12 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in 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 *Red rice extract 3%* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Red rice extract 3%* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected result (*positive/negative*) and the validation spectrum type (*A/B/C*).

	False positive	True positive	False negative	True negative
<b>Type A</b>	0	85	0	1549
<b>Type B</b>	0	35	0	4659
<b>Type C</b>	0	0	0	34

The substance/substance group *Red rice extract 3%* can be clearly distinguished from all other substances. In order to make these figures comparable, the weighted *true negative rate (specificity)* and the weighted *true positive rate (recognition rate)* are determined:

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5843 %)	100.0000 % (> 92.9412 %)
<b>Type B</b>	100.0000 % (> 99.8304 %)	100.0000 % (> 82.8571 %)
<b>Type C</b>	100.0000 % (> 79.2424 %)	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
90076	90076	0.00	34.61
90090	90090	0.00	35.98

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 1.3-2017-06

Validated substance/substance group **Vitamin C**  
Substance class BioG MicroTabs  
Report date 17/11/2017  
Report number 90020-2017-11-17  
Executing company HiperScan GmbH  
Weißeritzstraße 3  
01067 Dresden  
Germany

### Relevant substance names

Vitamin C

### Special notes

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

*no information*

### Applicable documents

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

### Validation method

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

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

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

### Calibration samples

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

Supplier	Substance	Batch	Sample ID	Spectra	Certificate
Biogenics	Vitamin C	BG15235	90107	40	from supplier
Biogenics	Vitamin C	BG15235	90108	40	from supplier

## Validation samples

A total of 6383 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 *Vitamin C*. These samples are listed above in the [calibration samples](#) section.
- 1554 spectra from a total of 20 batches from further 19 substances. These spectra were recorded by *HiperScan GmbH*. *Type A* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type A* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix A](#). The samples in [Appendix A](#) were added for model generation not with the intention to have the model identify these substances, but with the intention to make the model reject them despite their similarity to substances identifiable.

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

These samples are allowed to originate from the same batch as calibration samples (*Type A*) as long as the 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 *Vitamin C*.

Supplier	Substance	Batch	Sample ID	Spectra
Biogenics	Vitamin C	HG8002	90020	40
Biogenics	Vitamin C	HG8002	90065	40
Biogenics	Vitamin C	BG15235	90107 <sup>†</sup>	20
Biogenics	Vitamin C	BG15235	90108 <sup>†</sup>	20

- 4590 spectra from a total of 55 batches from further 61 substances. These spectra were recorded by *HiperScan GmbH*. *Type B* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type B* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix B](#).

**Type C** Spectra of independent samples not included in the database structure. *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 1 *Apo-Ident* customers from 1 batches from the substance/substance group *Vitamin C*.

Supplier	Substance	Batch	Spectra
Direkt	Vitamin C	FF0297	5

<sup>†</sup>These spectra were recorded from 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 1 *Apo-Ident* customers from a total of 11 batches from a further 11 substances. These spectra were recorded by *Apo-Ident* customers. *Type C* samples are documented within this entire report. If the substance can be identified with this [chemometric model](#), the samples are listed in the *Type C* section of each substance page. If the substance cannot be identified by this model, the samples are listed in [Appendix C](#).

## Validation results

The validation runs checked whether the substance/substance group *Vitamin C* can clearly be distinguished from all other substances using NIR spectroscopy with *Apo-Ident*. For this purpose, all relevant spectra of the various substances were compared with *Vitamin C* and it was evaluated how many matches (positive) and rejections (negative) were correct or incorrect. The following table breaks down the numbers of correct and incorrect results according to the expected 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	1554
<b>Type B</b>	0	40	80	4590
<b>Type C</b>	0	0	5	34

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

	Specificity	Recognition rate
<b>Type A</b>	100.0000 % (> 99.5857 %)	100.0000 % (> 92.5000 %)
<b>Type B</b>	100.0000 % (> 99.8248 %)	33.3333 % (> 30.8333 %)
<b>Type C</b>	100.0000 % (> 79.5022 %)	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
90107	90107	0.00	281.00
90108	90108	0.00	281.98

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 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.

## *Appendix A: Additional calibration samples (Type A)*

Not required.



## 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 67 batches. From these 2990 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
Biogenics	Amino acid mix PR5	pending	40	from supplier
Biogenics	Antioxidants mix	pending	40	from supplier
Biogenics	Betaine	BG0190	60	from supplier
Biogenics	Betaine	BG16024	60	from supplier
Biogenics	Betaine	pending	40	from supplier
Biogenics	Broccoli-B complex	HH8001	40	from supplier
Biogenics	Broccoli-B complex	HH8001	40	from supplier
Biogenics	Cardioprotective...	pending	40	from supplier
Biogenics	Cranmax / Cranbe...	FL0562	40	from supplier
Biogenics	Cranmax / Cranbe...	MRE0MM	40	from supplier
Biogenics	Cranmax / Cranbe...	FL0562	40	from supplier
Biogenics	Cranmax/mannose	BG15305	60	from supplier
Biogenics	Curcuma L. extr...	EB0106	40	from supplier
Biogenics	Ginkgo	HJ0167	40	from supplier
Biogenics	Ginseng	HJ0168	40	from supplier
Biogenics	Glucosamine sulf...	EB0218	40	from supplier
Biogenics	Glucosamine sulf...	EB0218	40	from supplier
Biogenics	Glucosamine sulf...	JA8006	60	from supplier
Biogenics	Glucosamine sulf...	JA8006	60	from supplier
Biogenics	Glucosamine sulf...	JA8006	60	from supplier
Biogenics	Glycine	BG16006	60	from supplier
Biogenics	Glycine	pending	40	from supplier
Biogenics	HMR lignans	pending	40	from supplier
Biogenics	HMR lignans	EK0413	40	from supplier
Biogenics	L-alanine	pending	40	from supplier
Biogenics	L-asparagine mon...	pending	40	from supplier
Biogenics	L-carnitine tart...	pending	40	from supplier
Biogenics	L-carnitine tart...	EPEHMM	40	from supplier
Biogenics	L-citrulline	pending	40	from supplier
Biogenics	L-glutamine	pending	40	from supplier
Biogenics	L-glutamine	BG16190	60	from supplier
Biogenics	L-histidine	pending	40	from supplier
Biogenics	L-isoleucine	pending	30	from supplier
Biogenics	L-leucine	pending	40	from supplier
Biogenics	L-leucine	BG15463	60	from supplier
Biogenics	L-lysine	EPEHMM	40	from supplier
Biogenics	L-lysine HCl	pending	40	from supplier
Biogenics	L-ornithine	EPEHMM	40	from supplier
Biogenics	L-phenylalanine	BG15514	60	from supplier
Biogenics	L-phenylalanine	pending	40	from supplier
Biogenics	L-proline	pending	40	from supplier
Biogenics	L-serine	pending	40	from supplier
Biogenics	L-threonine	pending	40	from supplier
Biogenics	L-tryotophan	BG15478	60	from supplier
Biogenics	L-tryotophan	MHMIMM	40	from supplier
Biogenics	L-tryotophan	MHMIMM	40	from supplier
Biogenics	L-tyrosine	pending	40	from supplier
Biogenics	Magnesium	BG15523	60	from supplier

*continued on the next page*

*continued from previous page*

<b>Supplier</b>	<b>Substance</b>	<b>Batch</b>	<b>Spectra</b>	<b>Certificate</b>
Biogenics	Methionine	BG15486	60	from supplier
Biogenics	Methionine	pending	40	from supplier
Biogenics	Natural amino ac...	BG16093	60	from supplier
Biogenics	Omega 3 DHA / EPA	GE8003	40	from supplier
Biogenics	Omega 3 DHA / EPA	GE8004	40	from supplier
Biogenics	Omega 3 DHA / EPA	GE8003	40	from supplier
Biogenics	Omega 3 DHA / EPA	GE8003	40	from supplier
Biogenics	Omega 3 DHA / EPA	GE8003	40	from supplier
Biogenics	Ornithine aspart...	pending	40	from supplier
Biogenics	Osteo (Cal/Mag/D...	pending	40	from supplier
Biogenics	SOD melon extract	BG16097	60	from supplier
Biogenics	Statine	46501	40	from supplier
Biogenics	Statine	46501	40	from supplier
Biogenics	Taurine	pending	40	from supplier
Biogenics	Valine	pending	40	from supplier
Biogenics	Vitamin E - Mixe...	FF0298	40	from supplier
Biogenics	Vitamin E - Mixe...	FF0298	40	from supplier
Biogenics	Vitamin E - Mixe...	FF0298	40	from supplier
Biogenics	Vitamin K2 MK-7	BG16096	60	from supplier

## 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 7 batches. From these, 21 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
Direkt	Cranmax / Cranberry e...	FL0562	2
Direkt	Curcuma L. extr. - Gi...	FJ0187	3
Direkt	Glucosamine sulfate ...	EB0218	3
Direkt	HMR lignans	EK0413	3
Direkt	L-tryptophan	MHELM	2
Direkt	Statine	46501	7
Direkt	Vitamin E - Mixed Toc...	FF0298	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):

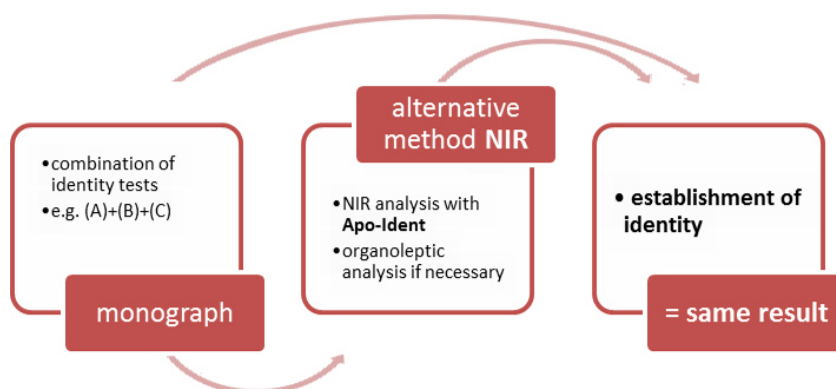
*“Validation is the provision of documented proof which with a high degree of safety documents that, via a specific process or standard work process, a medicinal product is manufactured and tested, which is in accordance with previously determined quality features.”*

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 2017-06* 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***

Alfatriadiol  
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



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