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NOTE FOR GUIDANCE ON THE USE OF NEAR INFRARED SPECTROSCOPY BY THE PHARMACEUTICAL INDUSTRY AND THE DATA REQUIREMENTS FOR NEW SUBMISSIONS AND VARIATIONS

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1. INTRODUCTION

1.1 Objective

This guideline is intended to provide guidance to companies in the process of calibration, validation and maintenance of a Near Infrared Spectroscopy (NIRS) method and the type of data to be submitted to the competent authorities in the case that NIRS is subject or part of an application.

1.2 Background

NIRS is a well established technique in the food, chemical, agrochemical and petrochemical industry, and has now also been used for many years in the pharmaceutical industry. The technique appears to be useful for the identification and assay of pharmaceutical substances, the identification and assay of such substances in the finished products, as well as for in-process control and for monitoring purposes. The principles of NIRS differ from usual conventional analytical techniques such as HPLC and GC. Like IR spectroscopy chemometric techniques are usually required for interpretation. NIRS has been described in the European Pharmacopoeia since 1997, however a single reference to this monograph is not considered sufficient for registration.

1.3 General concepts

Regulatory status

A NIRS method can be used as an alternate method to one or more validated methods specified in the quality part of the dossier (the reference methods). As a NIRS method generally needs to be developed and validated in conjunction with these reference methods and cannot easily be repeated by official control laboratories, these reference methods and corresponding specifications should remain included in the authorised specifications. Once the NIRS method has been approved by the competent authorities, the specification 'if-tested' may be added to the reference method. The NIRS method must be challenged with the reference method once a year to ensure its ongoing validity and the maintenance of the reference method, i.e. a sample of a batch should be analysed by both the reference method and the NIRS method and the results should be compared.

Submission of data

The type of data to be submitted to the competent authorities can be less extensive as described in this guideline, if justified with reference to the potential impact on public health. A declaration of the company that a NIRS method has been validated in conformity with this guideline may be sufficient for certain applications e.g. the use of NIRS as qualitative method for colouring materials and plastic primary packaging materials.

GMP

As different interpretations are present regarding the borderline between the data to be provided in the dossier for a marketing authorisation and GMP, this guideline will comment on this aspect where relevant

The apparatus should be laid down unambiguously. The level of detail should take into account the still limited transferability of a NIRS method. See section 4 for more information. Additional information may be necessary, e.g. with respect to sample temperature or humidity in the test room.

Performance verifications are considered GcLP or GMP, thus no limits for these verifications have to be provided in the dossier for a marketing authorisation.

2. QUALITATIVE METHODS

2.1 General remarks

Identification

In Pharmacopoeial monographs, identification is defined as the confirmation of a certain chemical entity. However the pharmaceutical industry uses a wider concept, implying that identification may also include differentiation between different qualities of one chemical entity (e.g. particle size, polymorphs). To allow differentiation, this guideline uses the terms identification (only chemical structure) and qualification (chemical- and physical attributes). Conventional identification is often based on more than one analytical method. Consequently it should be clear, if applicable, which reference method(s) will be replaced by the NIRS method.

2.2 Method development

Principle

The identification or qualification of a substance (drug substance, excipient, blend, drug product, intermediate) with NIRS is based on the comparison of the spectral data of this substance with the spectral data of several samples of several batches of different substances present in a reference library. Chemometrics will usually be necessary to compare the data and to draw conclusions (pass, no match or ambiguous). In case of an ambiguous conclusion, the method needs to be adjusted such that the substance will correctly be either approved or rejected, or those substances that interfere should be excluded from the scope of the method. Interfering substances or grades of substances may also be classified as one single entity if possible (e.g. different grades of lactose).

The classification of a substance can be done in several stages, e.g. first a classification of chemical identity or a group of related substances, and then application of more selective models for each individual grade or substance. This approach can be used to decrease the likelihood of false positives/negatives.

Chemometrics, spectral pre-treatments, wavelength range and thresholds

For the identification or qualification of pharmaceutical substances the combined use of the chemometric techniques Wavelength Correlation (WC) of the second derivative spectra and Maximum Wavelength Distance (MWD), both applied on the whole NIRS range (1000 – 2500 nm), is highly preferred.

Other combinations of chemometric techniques and pre-treatments are only acceptable if justified. Major advantages of WC methods are the ability to address a fixed value to the threshold and that individual methods and their thresholds can be compared, whereas methods based on Principal Component Analysis (PCA) are all unique being the result of the included substances and the choices made during the development of the method. Moreover it can be assumed that model updating is more straightforward for univariate methods like WC and

MWD than for multivariate PCA based methods. 'Smoothing' may be used as additional pre-treatment.

Chemometric thresholds should be determined in the process of method development. Unless justified, a threshold below 0.95 is not acceptable for WC of the second derivative. Insufficient turnover of substances leading to insufficient data is not regarded an acceptable justification, as NIRS is meant to be used as an alternative for frequent routine quality control.

Spectral library and calibration

For each substance for which the method is intended, three or more spectra of at least three batches (together called the training set) should be included in the reference library. These batches should be verified with the conventional reference methods, included in the specification, and represent the normal variation in suppliers, physical parameters etc. Validation of the method should demonstrate that spectra of an acceptable minimum number of batches have been included in the training set and that these batches are sufficiently representative to cover the normal variation of the substance. The composition of the reference library should be laid down in a list of batch numbers.

It should be verified that the spectra used to create the reference library are approved correctly using the developed calibration model.

Other applications

For in-process controls and monitoring purposes other methods may be more suitable, e.g. PCA based methods. The reliability of each chosen method should be demonstrated by appropriate validation according section 2.3. Depending on test type the validation may be less extensive.

2.3 Method validation

Principle

Validation of a qualitative NIRS method should consist of validation for specificity and robustness. After each step of this validation, the NIRS method may be adjusted if necessary. Possible adjustments are a change of pre-treatment and a change of thresholds, to expel substances from the scope of the method, or to classify substances as one. The results of the final validation should be submitted to the competent authorities.

Specificity

The extent of specificity testing depends on the application of the NIRS method. Lack of specificity of the NIRS method can be compensated by other supporting analytical procedures.

Independent samples of substances represented in the reference library, but not used to create it (i.e. different batches, blends), must be tested and all approved correctly (pass).

Potential challenges should be presented to the reference library. These challenges should be rejected (no match).

For the identification or qualification of pharmaceutical substances, relevant existing name- and structure analogues should be included in the external validation set, unless their absence is justified. Justification can be based on:

- The number of included analogues in view of the total number of existing analogues (the validation set should be sufficiently representative for the whole set of all existing analogues).

- The expected Near Infrared (NIR) spectral characteristics of the analogues.
- The probability of their presence in the concerned pharmaceutical setting.

Where applicable (e.g. qualification applications), validation should include challenge with different grades of the same substance, anhydrous/hydrated material or different polymorphs. Consideration should also be given to materials manufactured by external suppliers that could be delivered in error.

The results of the validation should demonstrate for each tested parameter unequivocally, that the NIRS method is sufficiently specific to discriminate between batches that comply with the tested parameter and batches that don't, in the same way as for the reference method.

The composition of the external validation set should be described unambiguously and should be justified. If a new NIR-spectrophotometer is introduced, maximum effort should be made to transfer the former validation set to the new spectrophotometer.

Robustness

Effects of possible, relevant variations, e.g. temperature (environment and sample), humidity, different position of the sample in the optical window, different sample presentation devices, probe depth or, if applicable, packaging materials, should be understood and documented. Instrumental variations can also be considered in the validation for robustness, e.g. changing lamps, reflectance standard etc. Some variations and potential changes can already be included in the calibration during the development of the method.

2.4 Change control

Method and instrumentation

Changes (both planned and unplanned), that might affect the performance of the method and may require re-validation, are more likely to occur with NIRS than with conventional analytical methods. This especially concerns the qualitative NIRS methods where spectra of batches are likely to be added to the reference library to keep it up to date and to a lesser extent to all NIRS methods in case of relevant changes to the instrumentation, which cannot be controlled with performance verifications alone.

Future changes to the NIRS method or instrumentation that have been dealt with according to an accepted change control protocol, can be regarded as falling within the scope of GMP and consequently need no variation application. Requirements on change control are presented in table 2.1.

Preferably, a suitable change control test is provided for each method or reference library. This change control test should be composed of a minimum of two standard sets (i.e. two classes or substances) for which separation is most critical. If the NIRS method does not comply with the change control test, it should be fully re-validated. It should be demonstrated that the performance of the change control test is stable over time.

Some potential changes, including changes to instrumentation, can already be included in the calibration. Robustness data from the validation experiments may demonstrate that some changes have no effect.

Software

Comparison of the chemometric results applied on the spectra present in the library with the old and new software is suitable as change control test.

Table 2.1 Change Controls

Change	Revalidation of library	Instrument performance controls*	Revalidation of method, or change control test
Change to the reference library:	Yes**	n/a	n/a
(addition or deletion of batches or substances)			
Instrumentation changes:	n/a		
- Software***		No	Yes
- Hardware****		Yes	Yes

* As Ph. Eur. 2.2.40

** Dependent on the chemometric technique re-validation is sometimes not needed when substances are expelled from the method.

*** New software or new version of existing software.

**** E.g., lamp, optical- and electronic components, sample presentation module, location, instrument upgrade or replacement

n/a Not applicable

3. QUANTITATIVE METHODS

3.1 General remarks

Pre-conditions

A NIRS quantification should always include a qualification of the suitability of the sample to be quantified with the proposed method. This qualification method should reject samples that are either out of range or out of the specifications that have been taken into account in the calibration. It is recommended that this qualification is done according to those procedures detailed in section 2. Other procedures may be used, if justified.

Calibration and validation

NIRS methods to be used for quantification require calibration of the NIR spectral response against verified reference data or against data from samples especially prepared for the calibration. Therefore, some characteristics of the reference method should be considered in the process of development and validation of the NIRS method, e.g. accuracy, range, and precision. The reference method should be used as described in the dossier for Marketing Authorisation in order to be able to compare the accuracy. The calibration set should be independent from the validation set (i.e. the validation set should include data from other batches than the batches already included the calibration set). For both sets, the selection criteria should be presented.

3.2 Method development

Calibration range

The calibration range should be wider than the specified range and not too small in view of the Standard Error of Laboratory (SEL) of the reference method. This SEL concerns the intermediate precision (intra-lab) or reproducibility (inter-lab), whichever is applicable.

Calibration set

The calibration set should be selected such that it covers the full variation in the sample, including differences in physical properties. Because the calibration range should be wider than the specified range (and thus the normal production range), samples with amounts of the quantified substance out of specification should be included. Development samples or samples made on purpose are normally required. If samples are made specifically, the variation in composition should preferably be established for all components in order to cover matrix effects. It is recommended that an appropriate design of experiments should be considered, in order to produce a sensible and sufficient number of samples encompassing potential matrix effects. Suitable consideration should be given to the levels by which components are modified. Correlations between variations in the substance to be studied and other components should be checked and minimised. The selected calibration samples and calibration batches should preferably have an even (rectangular) distribution across the calibration range. This selection and the number of calibration samples and batches should be sufficient to generate a calibration model of good predictive ability. This should be demonstrated in the process of validation.

Calibration model

The choice of the calibration model should be justified, including a rationale for the selection of the pre-processing, wavelength(s) or wavelength range, and chemometric technique. The results of the calibration should be submitted as a list of batch numbers with related results. The chosen model should be laid down and presented in detail, including the equation (i.e. for Multiple Linear Regression (MLR) based methods) or a specific identifier such as filename and date (i.e. for Principal Component Regression (PCR) and Partial Least Squares (PLS) based methods).

The performance of the calibration should be quantified and assessed in relation to the reference method. This should be done by determination of the Standard Error of Calibration (SEC) for MLR- and PCR based methods or the Standard Error of Cross validation (SECV) for PLS based methods, the number of outliers, and as a plot *NIRS predicted value* vs *reference method value*.

$$SEC = \sqrt{\frac{\sum_{i=1}^{n} (y_i - Y_i)^2}{n - p}}$$

n = number of batches

p = number of coefficients, i.e. wavelengths (MLR) or principal components (PCR) used

Y = NIRS predicted value

y = reference method value

It is pointed out that, for the determination of the SECV, spectra from samples of the same batch should be included or excluded from the calibration as group.

The relevant parameters, like slope and y-intercept, of the plot *NIRS predicted value vs. reference method value* should be presented. Theoretically these values should be one (1) and zero (0) respectively.

3.3 Method validation

Validation set

The validation set may comprise only production batches, or include both production and development batches. The set should cover variations up to but not exceeding the extremes of the calibrated range. The number of batches should preferably be identical to that of the calibration set, however a split 2/3 (calibration set) to 1/3 (validation set) is also acceptable. Ideally there should be an equal number of concentration points on either side of the nominal concentration of the calibration.

Linearity and accuracy

The results of the validation should be submitted as a list of batch numbers with related results and a plot *NIRS predicted value vs. reference method value.* The relevant parameters slope and y-intercept of the regression line should be submitted. Theoretically these values should be one (1) and zero (0) respectively. Alternative statistical methods, for validation of linearity, are also acceptable, if justified.

Accuracy can be determined by comparison with the reference method or with true samples (e.g. samples of placebo with added amounts of the tested substance). This latter option is however seldom applicable as other variations than the content of the tested substance can affect the result. Accuracy should be studied by determination of the Standard Error of Prediction (SEP) and the number of outliers of the validation set. The determined SEP should also be assessed in relation to the SEC or SECV and the precision of the reference method illustrated as the SEL_{ref} , intermediate precision (intra-lab) or reproducibility (inter-lab), which ever is applicable. The SEP and SEC or SECV should be comparable. The SEP_{nirs} should not be larger than 1.4 x SEL_{ref}, unless justified in view of the required accuracy of the test method.

$$SEP = \sqrt{\frac{\sum_{i=1}^{n}\left(y_i - Y_i\right)^2}{n}}$$

n = number of batches

Y = NIRS predicted value

y = reference method value

$$SEL = \sqrt{\frac{\sum_{i=1}^{m}\left(x_1 - x_2\right)^2}{m}}$$

m = number of batches

x1 –x2 = the absolute value of the difference between values measured at different laboratory conditions

Demonstrated linearity of the plot *NIRS predicted value vs. reference method value* (see above) and results of the paired t-test also provide information on the accuracy of the method. Determination of the SECV with the combined calibration- and validation set may also be used to provide information on the performance of the method. For this purpose, spectra from samples of the same batch should be included or excluded as group.

Specificity

The method should be challenged with samples resulting from possible deviations throughout the manufacturing process, e.g. samples where the amounts of ingredients (active substances and/or excipients) deviate from the normal production range and samples with deviating physical characteristics, e.g. water content. The method should also be challenged with forced -degraded samples and in the case of quantification of the active substance, with samples containing a different active substance (preferably a structure analogue). The results of the challenge should read that either these other samples will be rejected in the qualification step of the sample (see 3.1. *pre-conditions*) or that the concerned deviations from normal production do not interfere with the quantification in the calibrated range for the substance to be studied. If variation of the content of other substances within certain ranges is included in the calibration, then the method can be considered validated towards specificity for variation of these other substances within that range.

In addition information from the calibration may be used, examples given below:

- To what extent the variance in the reference data is covered by the factors used
- The wavelengths used in the calibration can be compared to the known bands of the analyte of interest and to those of the matrix to verify that the bands of the analyte of interest are being used in the calibration.
- Wavelengths used for the calibration (i.e for MLR models) or the loadings for the factors used (i.e. PCR or PLS models) can be examined to check if they are using the actual spectroscopic information from the analyte of interest.
- For PCR and PLS calibrations, the coefficients can be plotted and the regions of large coefficients be compared with the spectrum of the analyte.

Other means of demonstrating specificity should be justified.

Precision

Repeatability should be assessed by three replicates of three different concentrations or alternatively by a minimum of six determinations with a formulation containing 100% of the specified amount. For intermediate precision and reproducibility the effects of random events on the precision of the analytical procedure should be established. The standard deviation, relative standard deviation and confidence interval should be reported for each type of precision investigated. The precision should be equivalent or better than the reference method.

Robustness

See 2.3

3.4 Change control

If a quantitative method is changed (e.g. change of the calibration set) it should be fully re-validated. If the change concerns only instrumentation or software, see section 2.4.

The reference method can be used as change control test. The NIRS method and the reference method can be compared e.g. with a paired t-test. A minimum of six batches should be included in the t-test to demonstrate that no significant differences exist between the methods.

4. DATA REQUIREMENTS FOR NEW SUBMISSIONS AND VARIATIONS

In table 4.1 (see the next three pages) the data to be forwarded are listed. In the table is also indicated when variations to the method are subject for a variation application and which data should be submitted to the competent authorities for such applications.

Table 4.1

Topic	To be included in registration file	Changes subject for a variation application	Information to be submitted for a variation
DESCRIPTION OF THE METHOD			
Instrument	Yes		
- **Spectrophotometer**		No*	
- **Light source**		No*	
- **Monochromator, if applicable**		No*	
- **Detector**		No*	
- **Measurement technique, i.e. reflectance, transmission, etc.**		Yes	Full description and validation of the changed method
- **Other relevant settings**		No*	
Software (type and validation)	Yes	No*	
Tested specification	Yes	Yes	Full description and validation of the changed method
Qualitative method - **Wavelength(s) -range** - **Spectral mathematical pre-treatment** - **Chemometric techniques** - **Thresholds** - **Justification for selected wavelength(s) -range, pre-treatment, chemometric techniques and thresholds**	Yes	Yes	Full validation of the changed method and/or changed justification

Table 4.1, continued

Topic	To be included in registration file	Changes subject for a variation application	Information to be submitted for a variation
Quantitative method - **Wavelength(s) -range** - **Spectral mathematical pre-treatment** - **Chemometric technique** - **Equation or identifier of method** - **Justification for selected wavelengths -range, pre-treatment and chemometrics**	Yes	Yes	Full validation of the changed method and/or changed justification
Sample analysis	Yes		
- **Site / location**		No*	
- **Sampling**		Yes	Full validation of the changed method
- **Sample preparation**		Yes	Ditto
- **Sample presentation**		Yes	Ditto
- **Number of scans**		Yes	Ditto
CALIBRATION			
Spectral library (qualitative method)			
- **Selection criteria for included batches**	Yes	Yes	Description and justification of changed criteria.
- **Method of listing**	Yes	Yes	Description of changed method
- **Composition and results****	Yes	No*	
Calibration set (quantitative method) - **Selection criteria for the composition** - **Composition of calibration set** - **Results of the calibration**	Yes	Yes	Full description of changed calibration set and results of full validation.

Table 4.1, continued

Topic	To be included in registration file	Changes subject for a variation application	Information to be submitted for a variation
VALIDATION			
Qualitative method	Yes		
• **Specificity**			
- **Composition of the validation sets (both independent batches and potential challenges)**		No	
- **Rationale for the composition of the validation set (challenges)**		Yes	Description and justification of changed rationale.
- **Results of the validation**			
• **Robustness**		n/a n/a.	
Quantitative method • **Specificity** • **Linearity** • **Accuracy** • **Precision** • **Robustness**	Yes	n/a.	
CHANGE CONTROL			
Change control method or other change control aspect	Yes	Yes***	Description and justification of changed change control.

* It is pointed out that for many items changes are considered as no subject for a variation request based on the assumption that an adequate change control is included in the dossier. If this is not the case, such a change to the method should still be subject for a variation application or an appropriate change control method should be provided as request for variation.

** Results (e.g. correlation's) may be presented in tabulated and/or graphical form (e.g. calibration plots, PCA plots)

** * Only changes in definition of the change control should be applied for by variation. The changes itself do not always need to be approved through a variation.

n/a. Not applicable

5. GLOSSARY

Ambiguous conclusion	The sample is considered identical to more than one entity present in the reference library.
Calibration	The process of creating a model relating two types of measured data; for NIRS methods a model that relates concentrations or properties to absorbance spectra for a set of reference samples (the reference library or the calibration set)
Calibration set	The set of samples used for creating the calibration model
Change control protocol	A protocol listing potential future changes in the method and the actions considered necessary to prove the maintained reliability of the method.
Change control test	Test used to demonstrate unchanged method reliability following a change in a method.
Chemometrics	Mathematical multivariate methods to analyse/compare data
Maximum Wavelength Distance	A spectral reading is taken and the difference is calculated from a mean spectrum constructed from the set of library spectra constituting a given identity or grade. Then the difference at each wavelength is normalised by the library set variation at the same wavelength. Then the maximum normalised difference is taken as the distance of measure.
MLR	Multiple Linear Regression
No match conclusion	The sample is not considered identical to any entity in the reference library
Pass conclusion	The sample is considered identical to an entity in the reference library.
PCA	Principal Component Analysis
PCR	Principal Component Regression
PLS	Partial Least Squares Regression
Performance verifications	Tests to control the instrument performance
Pre-treament	Processing of the spectral data, with mathematical or other techniques, prior to chemometric analysis.
Qualification attributes	Characterisation based upon chemical- and physical
Qualitative method	Method with a ‘yes’ or ‘no’ result, e.g. identity.

Quantitative method	Methods with a numerical result, e.g. assay
Reference library	Database containing spectra of several batches of several substances to be tested. Spectra of unknown samples are compared with this database.
Reference method determine	The conventional analytical method that is used to the concentration or property value of the samples
Threshold	Limiting value, for qualitative methods, decisive for a "pass" or a "no match" conclusion
Training set	The set of samples, included in the reference library, that concern the same entity (substance or property value)
Validation set	Set of samples used in validating the model.
Wavelength Correlation	The correlation between spectra, i.e. the sum of the individual correlations of absorbances of each included wavelength.