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Committee for Human Medicinal Products (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

Addendum to EMA/CHMP/CVMP/QWP/17760/2009 Rev 3: Defining the Scope of an NIRS Procedure

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The latest revision of the 'guideline on the use of near infrared spectroscopy by the pharmaceutical industry and the data requirements for new submissions and variations' introduces the concept of the NIRS procedure **scope**, to facilitate continuous improvement and life cycle management.

Changes *within* the approved scope of the NIRS procedure are subject to GMP only. Changes *outside* of the approved scope of the NIRS procedure are subject to variation application. The definition of the scope is given in Section 4.1.1 of the guideline and the use of this scope to manage change control is further explained in Section 7 of the guideline.

As the concept of the NIRS procedure scope is new, this addendum has been produced to give a fictitious example of the scope for an NIRS procedure used for release testing for assay and content uniformity of the active substance in a finished product (uncoated tablet) and how changes to this scope would be managed according to the guideline.

Table 1 gives the method scope for the approved NIRS procedure.

Table 2 details those changes that would be considered WITHIN the scope of the procedure; therefore, maintained under GMP only.

Table 3 details those changes that would be considered OUTSIDE of the scope of the procedure: therefore, subject to variation application.

Table 1: Approved method scope for an assay and content uniformity NIRS procedure

Parameter	Procedure scope
Instrument	Foss XDS Masterlab: 3010-1019 Foss XDS sampling module: 3010-0954
Software	Foss Vision Version 1
Mode	Transmission
Scan Rate; Number	30/second; number of scans 150
Sample presentation	At-line sample trays customised for the tablet shape (40 tablets)
Concentration range	75-125 %
Spectral pre-processing	- Standard normal variate (SNV) - 15 points Savitzky Golay 2^{ND} derivative on 800-1130 nm
Spectral quality check algorithm	Mahalanobis distance (MD) and residual variance (RV)
Spectral quality check algorithm threshold	MD: max match value +1x standard deviation RV: max match value +3x standard deviation
Chemometric algorithm	PLS
PLS model parameter	PLS spectral range: 1030-1140. Number of latent variables: 4
Statistical attributes	SEP Bias Slope Intercept
Reference method	Method code-0032 (HPLC method using UV detection)

Table 2: Changes within the scope of the approved NIRS procedure

Please note:

- 'NA' means that change cannot be implemented without prior regulatory approval;
- A change can occur solely or in combination with other changes.

Parameter	Change that can be made within the scope
Instrument	Foss XDS masterlab: 3010-1019 (no change) Foss XDS sampling module: 3010-0954 (no change) Change lamp (to same type, for maintenance) Change detector (to same type, for maintenance) Change spectrophotometer (same vendor) if demonstrated in reproducibility tests
Software	Changed to Foss Vision Version 2
Mode	NA
Scan Rate; Number	Changed to 40/second or 20/second and / or number of scans changed to 100 or 200, if already demonstrated in robustness studies
Sample presentation	Change of size of at-line sampling trays customised for the tablet shape (60 tablets or 30) if already demonstrated in robustness studies
Concentration range	NA
Spectral pre-processing	NA
Spectral quality check algorithm	NA
Spectral quality check thresholds	MD: max match value +1x standard deviation (no change) RV: max match value +2x standard deviation (changed from 3 to 2)
Chemometric algorithm	NA
PLS model parameter	PLS spectral range: 1030-1120 (range tightened) Number of latent variables: 4 (no change) Change to introduce new samples to the calibration model (outliers, OOS) compliant with the scope of the procedure
Statistical attributes	Met (no change to requirements)
Reference method	Method code-0032 (Changes to the reference method within Ph. Eur. tolerances, for which the principle of operation has not changed)

Table 3: Changes outside of the scope of the approved NIRS procedure

Note: for proposed changes with a Type IA categorisation, the conditions associated with the relevant variation class (and as defined in the variations guideline) should be met; otherwise, variations should be submitted as Type IB. Proposed changes with a Type IB categorisation may be the subject of a post approval change management protocol, with consequential downgrade of the variation type.

Clarification regarding specific Type 1A variation conditions applicable to **all** parameters in Table 3 are given below:

- Condition 1: equivalent method performance (i.e., same acceptance criteria for analytical validation parameters such as SEC/SEP, Bias, Range, and outcomes) is demonstrated.
- Condition 3: at a minimum, the change is within the design specification of the equipment.

Additional interpretation specific to certain parameters for NIRS methods is given in Table 3 below.

<u>Considerations for veterinary drug substances and products</u>

For veterinary active substance and medicinal products a similar approach can be followed, further details can be found in the relevant guidelines on variations for veterinary medicinal products : Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations (EMA/CMDv/7381/2021) and COMMISSION IMPLEMENTING REGULATION (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council as amended.

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Parameter	Changes considered beyond the scope of the procedure	Type of variation	Considerations regarding conditions to be fulfilled
Instrument	Change of vendor, e.g., to ABB FT NIR	*Type 1A variation (B.I.b.2.a or B.II.d.2.a)* *Equivalent to VNRA B.12.a for veterinary products*	*Condition 3: same principle is used (e.g., spectrometer type, optical bench, multiplexer).*
Software	Change of vendor, e.g., to GRAMS 9.0	*Type 1A variation (B.I.b.2.a or B.II.d.2.a)* *Equivalent to VNRA B.12.a for veterinary products*	*Condition 1: at least equivalent method parameters are used.*
Mode	Changed to reflectance	*Type 1B variation (B.II.d.2.d)* *Equivalent to VRA F.II.d.2.b for veterinary products*	
Scan Rate; Number	Changed to 40/second or 20/second and / or number of scans changed to 100 or 200, if not demonstrated in robustness studies	*Type 1A variation (B.II.d.2.a)* *Equivalent to VNRA B.12.a for veterinary products*	
Sample presentation	Change to on-line measurement rather than at-line	*Type 1B variation (B.I.b.2.e or B.II.d.2.d)* *Equivalent to VRA F.I.b.2.b or VRA F.II.d.2.b for veterinary products*	
Spectral pre-processing	Changed to: - 10 point Savitzky Golay 2ND derivative on 800-1130 nm - Multiple Scatter Correction (MSC) with first derivative	*Type 1A variation (B.I.b.2.a or B.II.d.2.a)* *Equivalent to VNRA B.12.a for veterinary products*	*Condition 3: no change to the principle (e.g., the type of algorithm)*
Spectral quality check algorithm	Changed from PLS to SIMCA	*Type 1A variation (B.I.b.2.a or B.II.d.2.a)* *Equivalent to VNRA B.12.a for veterinary products*	*Condition 1: at least equivalent method discriminating power*
Spectral quality check	MD: max match value +2x standard	*Type 1A variation (B.I.b.2.a or*	*Condition 3: no change to the principle (e.g.,*

Parameter	Changes considered beyond the scope of the procedure	Type of variation	Considerations regarding conditions to be fulfilled
threshold	deviation (change to widen) RV: max match value +3x standard deviation (no change)	*B.II.d.2.a)* *Equivalent to VNRA B.12.a for veterinary products*	*the type of algorithm)*
Chemometric algorithm	MLR, PCR	*Type 1A variation (B.I.b.2.a or B.II.d.2.d)* *Equivalent to VNRA B.12.a for veterinary products*	*Condition 1: at least equivalent method discriminating power*
Model parameter	Changes such as: - Spectral range change: 1020-1170 - Number of latent variables: 5 (change from 4)	*Type 1A variation (B.I.b.2.a or B.II.d.2.a)* *Equivalent to VNRA B.12.a for veterinary products*	*Condition 1: changes were evaluated during development (robustness)*
Statistical attributes	Widened beyond initial approved statistical attributes	*Such a change would not generally be submitted in isolation and would be related to another change. The change in statistical attributes would therefore be considered under the variation for the related change.*	
Reference method	Method reference-0050 (change in detection mode e.g., UV replaced by fluorescence, a change in mode of operation) or Method reference-0032 (Changes outside Ph.Eur. tolerances)	*Implications for the NIRS procedure (e.g., its revalidation over time and the need for a change to the reference method stated in the scope of the NIRS procedure) should be considered under the related variation for the change in reference method*	

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