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Overview of comments received on "Addendum to EMA/CHMP/CVMP/QWP/17760/2009 Rev 3: Defining the Scope of an NIRS Procedure"

(EMA/CHMP/CVMP/QWP/17760/2009 Rev 3)

Name of organisation or individual	General or Specific comment	Line from (line nr. or 0 for general comment)	Line to (line nr. or 0 for general comment)2	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Outcome (To be completed by the Agency)
AnimalhealthEurope	General comment	0	0	AnimalhealthEurope would like to thank the CVMP for this Draft guideline and is grateful for the opportunity to comment. Please find some comments below. Should you have further questions, AnimalhealthEurope is happy to provide any clarification needed.	Comment noted.
AnimalhealthEurope	Specific comment	29	29	Comment on table 1: Spectral pre-processing: spectral pre-processing is performed on the range 800-1130 nm but later the spectral range of PLS model is given 1030-1140. This is outside the pre-processed range. It is unclear why the model development will happen outside the pre-processed range. Please clarify	Corrected in various places.
AnimalhealthEurope	Specific comment	37	37	Comments on table 2: • Would any 'within scope' changes, method verification be performed and pick up any method performance issues? Table 3 has text regarding method performance equivalence (condition 1 for Type 1A) however there is no such statement in Table 2. Would this be a default requirement for any 'within scope' change also? This may already be clear in the main document and therefore excluded in this addendum. It might be helpful to add such text before table 2 in this addendum. • Instrument: Changing the Lamp, Detector, or Spectrophotometer – May need performance Qualification and recalibration. However, such requirements need to be more explicit. • Software: Changing Software to Foss Vision Version 2 - No mention on ensuring software upgrade incompatibility with existing data management systems and how companies must handle the change reporting needs to be more explicit. • Scan Rate: Change in Scan Rate and Number- May affect signal-to-noise ratio and resolution. In such cases, existing SOPs/methods may need to be updated. How these changes will be handled needs to be clarified. • Sample preparation: The sample presentation example as worded is confusing. Changing the size of customised tablet tray would most likely not have been included in robustness. Customized trays (which may be common for animal health applications due to the shape & size variations in a product) for specific tablet shapes might not be suitable for other sample types, reducing versatility. Therefore, it is unclear why this is in scope for tray changes for animal health products. Please clarify. • Spectral quality check thresholds: Change in Spectral Quality Check Thresholds: Adjusting thresholds for the spectral quality check might increase false rejections. Therefore, circumstances where this change is necessary, need to be outlined. • PLS Model Parameter: Change in PLS Model Parameter Spectral Range: Tightening the spectral range could exclude relevant spectral information, potentially affecting the model's predictive accuracy. In such cases, the "what-if" isn't clearly outlined. Changing the PLS range will have a direct impact on the model performance. This example is quite a small range tightening however it should be avoided to be interpreted that any range tightening is acceptable. As this is an example, no major concern, however, some may take this as more than just an example. A major range change, even tightening, would most likely impact	The comments are helpful. However, proposals are out of scope of the current revision which focuses on table 3.

AnimalhealthEurope	Specific comment	58	58	Comments on table 3: • Mode: The mode of spectral acquisition is changed from transmission to reflectance. Changing the mode does changes the absorbance intensity as well as path length correction needs to be applied for the reflectance measurement. This is not mentioned clearly in the document. The pre-trained model might not understand this difference. Therefore, mode of data acquisition (from diffuse reflectance to transmission or vice versa) will invalidate the calibration curve. Hence such changes must be out of scope. • Spectral pre-processing: Changing pre-processing steps does have an impact on predictive accuracy. Are these preprocessing methods mentioned in Table 3 tested before for their impact on accuracy? However, the proposed guidance change does not cover protocol for changing the pre-processing technique and how to handle the impact to predictive accuracy. Please clarify. • Chemometric algorithm: Chemometric algorithm to be changed from PLS to MLR or PCR. Changing this completely changes the validated model. Is retraining and validation of models happening again? PLS & PCR models rely on dimensionality reduction while MLR uses single or Multiple functional group/attribute specific absorbance. Therefore, without model retraining and recalibration, such switch cannot occur. • Model Parameter: The comment with Condition 1 is not clear. It is unlikely that you would have included spectral range change or change to number of latent variables in validation robustness studies, though it would have been part of development to support the decision on the model parameters to take forward into validation. For this example, you would likely have built models for 3-6 variables and 4 LVs were then selected as the optimal parameter for method validation. Having this data from method development, in no ways supports later changing to a different number of LVs and it is very unlikely that a model with a different number of LVs would meet the method performance equivalence condition. We do not think that the statement following Condition 1 are helpful here. It can be removed, and the information would still stand. Changes to model parameters are acceptable as Type1a when model performance is demonstrated to be equivalent (condition 1).	The addendum does not define considerations related to specific changes, for example the activities required to change the mode of spectral acquisition are not defined and are a matter for assessment and/or inspection. It is for the applicant/MAH to justify their approach. Regarding the comment on model parameter, other change apart from number of LVs are possible, and so the condition text is retained.
JRP_MSD	General comment	0	0	Really like this addition, defining NIRS procedure by scope and giving examples will be very helpful.	The NIRS scope was defined in the original guidance. Thank you for the endorsement.
JRP_MSD	General comment	0	0	In a future update, would you please add more guidance regarding libraries for qualitative analysis? Specifically how to incorporate variability and what to do in cases where there is no reference standard or suitable reference method (non-defined media components, for example).	Comment noted.
JRP_MSD	Specific comment	32	39	Table Row for Instrument: Make component parts that can be changed without impacting scope less specific, to allow for more complex PAT instruments.	This section is extant and thus out of scope.
JRP_MSD	Specific comment	32	39	Table Row for Parameter - Software: Add caveat that software versioning must have no impact to scope.	This section is extant and thus out of scope.
JRP_MSD	Specific comment	32	39	Table Row for Parameter - Software: Allow for changes to equivalent software or additions of controller software such as SIPAT, if there is no impact to scope.	This section is extant and thus out of scope.
JRP_MSD	Specific comment	45	45	Add "meets change management test requirements," for qualitative procedures, since this demonstrates that there is no impact because of the scope change.	This is an expectation under GMP, no change needed.
JRP_MSD	Specific comment	58	58	Add change to sample preparation with potential to impact results, such as sample dilution reagent or vial composition.	Too detailed for this example, no change.
EFPIA	General comment	0	0	Positive reflections • Overall, a really positive update which will allow companies much more flexibility to rapidly implement model updates. This will facilitate continuous improvement and reduce time spent running sub-optimal methods. • Good choice of highly relevant example.	Comment noted.
EFPIA	General comment	0	0	Applicability • Could EMA clarify whether the guidance and in particular variation categories are applicable to biologics? (i.e., Categorization of Type IA and Type IB can be applied as described regardless of modality)? • Could EMA clarify whether the guidance is applicable to other types of spectroscopy, particularly Raman? • It is felt that the guidance is more suited to off-line and end product testing methods and does not adequately reflect the requirements of in-line NIR methods. • The example is quite limited, it would be helpful for EMA to provide additional guidance on specific scope elements not explicitly described in the case study.	IA changes may be applicable to biologics in certain circumstances based on conditions in EU variation classification guidance (see e.g. B.II.d.2 condition 4). The scope of the NIR guideline states that "The chemometric principles described within this guideline may also be applicable to other analytical techniques". The revision of the Addendum is primarily limited to Table 3. The comment is noted but creating additional examples for in-line

EFPIA	General comment	0	0	Flexibility • The proposed variation requirements are still too high to allow fully flexible and rapid model updates, particularly for in-line and CDC type procedures and procedures in the early phases their lifecycle where frequent updates can be anticipated. Even a type 1A can be considered a burden and a disincentive to the use of NIR for in-line monitoring.	All IA changes listed can be reported as annual updates keeping the dossier up to date subsequent to changes.
EFPIA	General comment	0	0	Recurring specific points • Changes of software platform or vendor including PAT management systems should be implementable under GMP providing that equivalence is demonstrated as this does not impact spectral data or model performance. • It is requested that EMA provide clarification on how to handle subtraction of spectra from a model and recognition that, together with addition of new variation, this is a standard and accepted part of model maintenance. • It is requested that EMA provide clarification on requirements for the quality check algorithm. Specifically, are two always required as presented in the case study and what about other common types of algorithm. • Addition of new sample variation is likely to increase the number of latent variables required and therefore this should be implementable under GMP and not require a 1A variation. • Widening of the spectral quality threshold is likely to be required as additional sample variation is added. Therefore, both widening and tightening of the threshold should be implementable under GMP and not require a 1A variation.	data sets is a routine part of model maintenance, and is implicitly included in Table 2, "PLS model parameter" changes. The approach taken to spectral quality checks should be justified; in this example, a single spectral quality check algorithm with associated thresholds is used. Equally, the addition of new sample variation may not require a change to the number of LV. Regardless, the number of LV is often critical to method performance and so this information should be registered in the dossier. Equally, the addition of new sample variation may not require a change to the spectral quality threshold. Regardless, the threshold is often critical to method
EFPIA	General comment	0	0	The example used is quite dated, specifically in terms of the make and model of instrument and software used. Would EMA consider updating?	Update of the example is out of scope of this revision. No action taken, although comment noted.
EFPIA	General comment	0	0	Addition of new samples into the calibration model is mentioned in Table 2 but subtraction of samples is not mentioned. Subtraction of samples is often valid and can significantly improve model performance where calibration samples are no longer relevant and sit outside the range of current expected variability. For example, if a particular supplier of excipients or manufacturing site are no longer used. Would it be possible to add instructions for how such changes should be handled?	Addition and subtraction of spectra from data sets is a routine part of model maintenance, and is implicitly included in Table 2, "PLS model parameter" changes. No change.
EFPIA	General comment	0	0	It is understood that the update is limited to the addendum of the Near-Infrared Guidance, not to the main body of the guidance. Still, as the main guidances chapter 7.1 and 7.2 do not give specific guidance on the scope elements which require post-approval variation, the addendum serves as a quasi-reference for the specific elements that are registration-change relevant. Therefore, it would be very helpful if in tables 1, 2 and 3 more context is given to explain expectations which go beyond the specific examples (for example, because two spectral quality check methodologies are listed in the example, are always two spectral quality check methodologies expected for a NIR method?)	The comment is noted but not in the scope of this current revision.
EFPIA	General comment	0	0	The changes in the current update are limited to table 3, which lists the outof- scope items and their respective variation categories. It would be advisable to also consider the comments given on table 1 and 2 about the specific items in the scope of the method (described in main guidance sections 4.1.1, 4.1.2, 4.1.3) to see if change to specific elements of the "scope details'' could be included in the "in-scope" table 2.	The scope of the Addendum revision is primarily limited to Table 3. Changes to Tables 1 and 2 are out of scope. The comment is noted.
EFPIA	General comment	0	0	Still, the rules for changes beyond the scope of the procedure are too strict to allow flexible maintenance of NIR methods. It seems reasonable that mode, sample presentation and reference method should require a variation, but other parameters such as instrument, software, scan rate/number, spectral quality check algorithm/threshold, chemometric algorithm and model parameters should be able to manage within the pharmaceutical quality system and be subject for inspection.	All IA changes listed can be reported as annual updates keeping the dossier up to date subsequent to changes. Updates to the NIR model can be made without prior authorization. No change.
EFPIA	General comment	0	0	We would like to note that the principle EMA is applying under the addendum to NIR could reasonably be applied to other methodologies where instrument control (CDS system) and equipment design (transmission cell vs a reflectance cell etc.) can influence the validated ranges of the registered method. If EMA intends broader application of these principles in the future, a more general guidance may be warranted.	The comment is noted.
EFPIA	General comment	0	0	It is a good idea to show an example of method scope for a NIRS procedure. It is also a good idea to use assay and content uniformity as an example because both CQAs are part of a drug product specification.	The comment is noted.
EFPIA	General comment	0	0	The current example of a method scope is limited to an off-line NIRS method typically performed in the QC laboratory using laboratory NIRS equipment. However, this proposed scope does not adequately represent in-line NIRS methods that are performed at the manufacturing line using specialized NIRS equipment with fibre optics, probes, and flow-through cells. As the pharmaceutical industry advances towards continuous manufacturing of drug substances and products, there is a corresponding shift towards employing timely in-line Process Analytical Technology (PAT) rather than relying on off-line NIRS methods, which are not conducive to continuous manufacturing processes. It is, therefore, recommended that the Addendum should be improved with additional tables for an in-line or on-line NIRS method. If tables for in-line/on-line methods are not included in the final Addendum, the current Addendum should at least support changes that are relevant for these methods.	The comment is noted. However, adding additional examples is not in the scope of this revision. The concepts defined in the scope are applicable to in-line methods.

EFPIA	General comment	0	0	Developing a robust in-line NIRS method typically requires more calibration data from commercial-scale production compared to off-line methods. In practice, this often means that in-line methods may necessitate more frequent model updates than off-line methods, especially in the early stages of a model's lifecycle. It is, therefore, crucial to provide regulatory flexibility concerning model updating. If pharmaceutical companies cannot perform model updates within Good Manufacturing Practice (GMP) guidelines and are required to submit a variation for each update, it will impose a significant regulatory burden. This could potentially slow the adoption of in-line NIR technology within the industry, which in turn may negatively impact the modernization of pharmaceutical manufacturing, as well as the overall quality and innovation in the field. Finally, the submission of a Type 1A variation can in some instances be an obstacle for implementation of improvements and changes to the NIRS method. Therefore should changes that are associated with normal improvement activities of a NIRS method not be subject to a Type 1A variation or Type 1B variation.	The comment is noted. However, all IA changes listed can be reported as annual updates keeping the dossier up to date subsequent to changes without prior authorization. No change.
EFPIA	Specific comment	25	25	Clarify that type 1A variation as introduced more frequently are also valid for change to analytical methods using NIR for biologics products.	IA changes may be applicable to biologics in certain circumstances based on conditions in EU variation classification guidance (see e.g. B.II.d.2 condition 4).
EFPIA	Specific comment	29	29	Spectral Quality Check algorithm: Listing both MD and RV implies that two spectral quality checks need to be used. There can be cases where it is justifiable to only use one.	The approach taken to spectral quality checks should be justified. This is an example only. No change.
EFPIA	Specific comment	37	58	Software Change of Vendor: Change of data analysis software does not impact the quality of the spectral data (this is related to the spectrometer), rather this is a GMP (IQ/OQ) activity. The resulting spectroscopic model with the new software should be validated according to the original requirements.	Software change is considered relevant and changes should be reported.
EFPIA	Specific comment	37	37	It is unclear what introduction of new samples “compliant to the scope of the procedure means”? Specifically, the part “outlier,OOS” in the bracket is not fully clear what this means. Subtraction of samples is also a typical life cycle management activity for spectroscopic models and should also be in scope under condition 1.	The revision of the Addendum is primarily limited to Table 3. The comment is noted.
EFPIA	Specific comment	37	58	Adjustments of spectral quality thresholds should be permissible within the scope of the method (both widening and tightening)	The comment is noted but not agreed. Widening can be reported annually.
EFPIA	Specific comment	40	44	Current: The proposed changes may be the subject of a post approval change management protocol, with consequential downgrade of the variation type. Rationale: Implication that Type II variations would be out of scope for downgrade via PACMP even though it is solely due to the examples and variation classifications provided under Table 3.	There are no Type II variations defined in Table 3 and thus there is no requirement to specifically mention Type II variations in the context of a PACMP. It is well established that a PACMP can be used to downgrade a Type II variation
EFPIA	Specific comment	10	57	Rationale: The current addendum implies a “minimal” or parameter-based approach, implying that such approaches are the expectation. It is important to clarify that for enhanced or performance-based approaches, alternatives may exist.	The revision of the Addendum is primarily limited to Table 3. The comment is noted.
EFPIA	Specific comment	35	35	Line 35 states that "'NA' means that change cannot be implemented without prior regulatory approval;" in reference to certain parameters in Table 2, yet the same parameters in Table 3 are held to "Type 1A variation (B.I.b.2.a or B.II.d.2.d)" which indicates that the change can be implemented without prior regulatory approval.	Text revised for clarity.
EFPIA	Specific comment	37	37	There are many pharmaceutical companies that connect their NIRS equipment to PAT Management IT systems for improved operation and data handling. These PAT Management IT systems cannot operate with all commercial chemometric software packages and it may be necessary to change chemometric software. If the change is handled within GMP example wise fulfilling IT validation requirements and model validation requirements this should be sufficient to handle the change.	Software change is considered relevant and changes should be reported. IA variations do not prevent immediate implementation of changes.
EFPIA	Specific comment	37	37	The word already is removed because during the life cycle of a NIRS method it can be found out that changing scan rate can improve the method performance. Maybe the new scan rate was not part of the original robustness studies. It should be possible to test the robustness of a new scan rate after filing of the NIRS method to the Agency and change it within GMP.	The revision of the Addendum is primarily limited to Table 3. The comment is noted.
EFPIA	Specific comment	37	37	It is common practice to evaluate if other pre-processing methods improves method performance during model updating. There can also be developed novel preprocessing methods that was not well described or invented when the model was developed originally.	The revision of the Addendum is primarily limited to Table 3. The comment is noted.
EFPIA	Specific comment	37	37	It is important to recognize that if new samples that represent new variation is included during a model update it is likely that the number of latent variables can increase, and the optimal spectral region change. If the updated model still meets validation requirements and is compliant with the scope of the model this should not require a Type 1A variation.	The revision of the Addendum is primarily limited to Table 3. The comment is noted.

EFPIA	Specific comment	58	58	Spectral pre-processing and chemometric data analysis can be done in many different software packages or opensource software like Python. If any change in software is thoroughly tested and documented, it should not be subject to a Type 1A variation.	Not all software packages use the same algorithms and hence processed data may be different, impacting the applicability of the data. No change is made.
EFPIA	Specific comment	58	58	Specifically, during the development of an in-line NIRS method, there is limited knowledge of the manufacturing process variability. The scan rate is set to achieve both a fast-enough NIRS result and a result with sufficiently low variance to comply with the method's scope. As more process knowledge is gained, the scan rate can be optimized. Such a change should be implementable under GMP and not subject to a Type IA variation.	The scan rate directly impacts signal to noise and critical method attributes, e.g., sensitivity and precision. No change is made.
EFPIA	Specific comment	58	58	During model update studies it is common practise to test new pre-processing methods and settings. Optimized preprocessing and/or settings should comply with the validation requirements if the method. Such a change should be implementable under GMP and not subject to a Type IA variation.	New pre-processing methods and settings impact critical method attributes, e.g., robustness, accuracy. No change is made. The comment is noted.
EFPIA	Specific comment	58	58	The MD values will change and increase as models are updated with new spectral variation. This is common knowledge, and such a change should be implementable under GMP and not subject to a Type IA variation.	The spectral quality check impacts critical method attributes, e.g., robustness, accuracy, identity. No change is made. The comment is noted.
EFPIA	Specific comment	58	58	When more variation is encountered during the life cycle of the NIRS model and additional samples are added to the calibration data set it is foreseeable that the number of model parameters will go up. This is common knowledge, and such a change should be implementable under GMP and not subject to a Type IA variation.	data sets is a routine part of model maintenance, and is implicitly included in Table 2, "PLS model parameter" changes. The approach taken to spectral quality checks should be justified; in this example, a single spectral quality check algorithm with associated thresholds is used. Equally, the addition of new sample variation may not require a change to the number of LV. Regardless, the number of LV is often critical to method performance and so this information should be registered in the dossier. Further, the addition of new sample variation may not
GS	Specific comment	37	37	PLS model parameter If PLS spectral range is widened, and all other remained the same, would the change categorise as “NA”?	The revision of the Addendum is primarily limited to Table 3. The comment is noted.